26 October 2007 | $10

Science

ADVANCES IN NEUROSCIENCE

Decision Making

AAAS

Volume 318, Issue 5850

COVER

Decision-making involves the coordinated interaction of many brain areas, even for a rather simple game of chance. A special section beginning on page 593 examines the processes and structures that underlie decision-making—from trivial choices to major life-changing decisions.

Photo Illustration: Christopher Bickel and Kelly Krause/Science (photo by Jessica Newfield/Science)

DEPARTMENTS

EDITORIAL

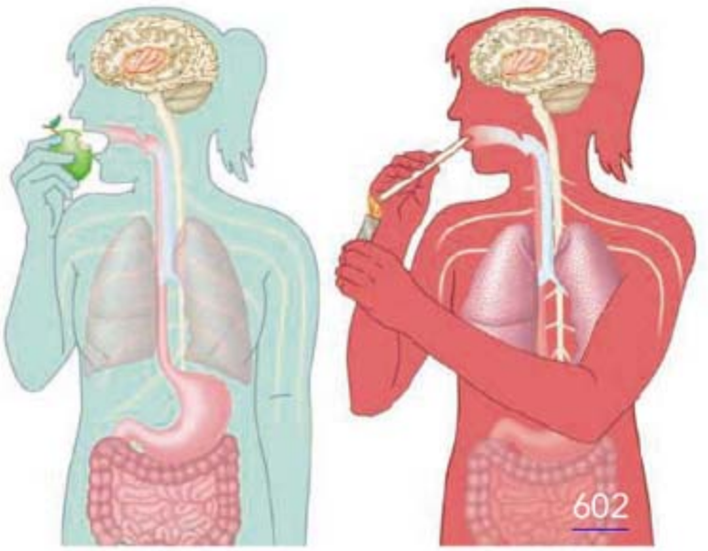
SPECIAL SECTION

Decision-Making

INTRODUCTION

REVIEWS

See also related Editorial page 533; News story page 553; Science Express reports by M. J. Frank et al. and F. A. Mansouri et al.; Science's STKE material on page 527 or at www.sciencemag.org/sciext/decisionmaking/



NEWS OF THE WEEK

NEWS FOCUS

Combating Malaria

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Science

SCIENCE EXPRESS

www.sciencexpress.org

NEUROSCIENCE

Hold Your Horses: Impulsivity, Deep Brain Stimulation, and Medication in Parkinsonism

M. J. Frank, J. Samanta, A. A. Moustafa, S. J. Sherman

L-dopa, a common treatment for Parkinson's disease, impairs certain forms of learning whereas deep brain stimulation inappropriately accelerates decision-making.

>> *News story p. 553; Decision-Making section p. 593*

10.1126/science.1146157

NEUROSCIENCE

Mnemonic Function of Dorsolateral Prefrontal Cortex in Conflict-Induced Behavioral Adjustment

F. A. Mansouri, M. J. Buckley, K. Tanaka

In monkeys, the lateral prefrontal cortex, but not the anterior cingulate cortex, is essential for making decisions in which conflicting information has to be evaluated.

>> *Decision-Making section p. 593*

10.1126/science.1146384

GENETICS

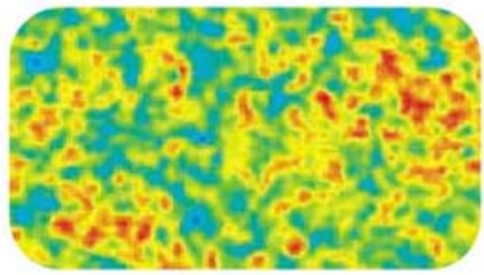
A Melanocortin 1 Receptor Allele Suggests Varying Pigmentation Among Neanderthals

C. Lalueza-Fox et al.

Neanderthals carried a variant of a skin cell receptor similar to that in modern European humans, suggesting that their pigmentation may have been similarly variable.

>> *News story p. 546*

10.1126/science.1147417



ASTROPHYSICS

A Cosmic Microwave Background Feature Consistent with a Cosmic Texture

M. Cruz, N. Turok, P. Vielva, E. Martínez-González, M. Hobson

An unusual cold spot in the cosmic microwave background has properties expected of a cosmic texture, a predicted relic of the decoupling of photons and atoms just after the Big Bang.

10.1126/science.1148694

STRUCTURAL BIOLOGY

GPCR Engineering Yields High-Resolution Structural Insights into β_2-Adrenergic Receptor Function

D. M. Rosenbaum et al.

Replacing part of the β_2-adrenergic receptor allows an accurate determination of the receptor's structure, showing how ligand binding activates G proteins.

10.1126/science.1150609

STRUCTURAL BIOLOGY

High-Resolution Crystal Structure of an Engineered Human β_2-Adrenergic G Protein–Coupled Receptor

V. Cherezov et al.

The 2.4 angstrom structure of the human β_2-adrenergic receptor displays an architecture and helical orientation distinct from that of rhodopsin, the prototypical member of this family.

10.1126/science.1150577

LETTERS

BOOKS *ET AL.*

EDUCATION FORUM

PERSPECTIVES

ESSAY

BREVIA

ECOLOGY

Showing unexpected resilience, tropical forests in the Amazon apparently increased photosynthesis in response to the 2005 drought, according to satellite measurements.

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PLANETARY SCIENCE

High-temperature grains formed near a protosun can be transported efficiently outward along the midplane of the early solar system, explaining how such grains occur in comets.

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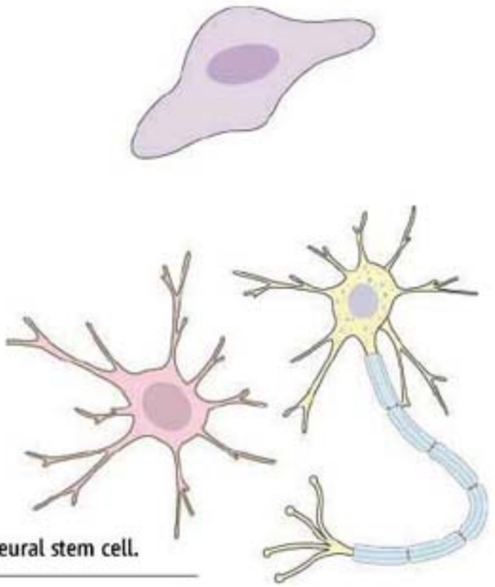
SCIENCENOW

www.sciencenow.org DAILY NEWS COVERAGE

Planet's CO_2 Production Surges
Growing world economy churns out more greenhouse gas than expected.

Reason for the Season
New study helps explain why flu is more contagious under wintry conditions.

Scent of a Hunter
Panicky pachyderms sniff out threatening humans.



Decisions of a neural stem cell.

SPECIAL SECTION

Decision-Making

SCIENCE'S STKE

www.stke.org SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT

EDITORIAL GUIDE: Focus Issue—Decisions, Great and Small
E. M. Adler and N. R. Gough
At the cellular level, neurons and their precursors face multiple decision points.

PERSPECTIVE: Neurons or Glia? Can SHP2 Know It All?
V. Coskun, J. Zhao, Y. E. Sun
The tyrosine phosphatase SHP2 may help regulate the balance between neurogenesis and gliogenesis.

PERSPECTIVE: Alchemy in the Soup—Transforming Metabolic Signals to Excitability
C. G. Nichols
ATP-sensitive potassium channels link cell metabolism to excitability in various tissues.

Getting the right start.

SCIENCECAREERS

www.sciencecareers.org CAREER RESOURCES FOR SCIENTISTS

GLOBAL: Mastering Your Ph.D.—Starting Off on the Right Foot
P. Gosling and B. Noordam
Getting into good habits early is key for grad students in starting a term off right.

MISCINET: Educated Woman, Postdoc Edition, Chapter 10—Loyalty, Subterfuge, Manipulation, and Sabotage
M. P. DeWhyse
Micella has only now realized how much the life of a postdoc can resemble a paperback thriller.

US: Tooling Up—Barriers to Decision-Making
D. Jensen
Those trained to make specialized decisions in the lab often make poor decisions in a job search.

US: From the Archives, Murder Most Foul—How Not to Kill a Grant Application
V. Mohan-Ram
Mystery writer Philip Marlowe blended real-life facts with intrigue and style—the same elements needed in competitive grant applications.

SCIENCEPODCAST

Download the 26 October *Science* Podcast to hear about impacts of soil erosion on the carbon cycle, impulsivity in Parkinson's patients, the debate over bed nets in Africa, and more.
www.sciencemag.org/about/podcast.dtl

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EDITED BY STELLA HURTLEY AND PHIL SZUROMI

<< The Makings of Self-Pollination

Plants that produce both male and female gametes use various strategies to determine whether they will predominantly self-fertilize or predominantly use pollen from other flowers. Although compatibility of cell surface receptors is part of the story, the geometry of flower parts also affects what pollen lands on the stigma. In the flower of the domesticated tomato, the stigma is buried within the anthers, which makes self-fertilization more likely. In wild relatives of the tomato, however, the stigma projects beyond the anthers and favors cross-fertilization. **Chen *et al.*** (p. 643) now identify the gene that regulates the length of the style, and thus regulates the relative geometry of stigma and anthers in the tomato.

A Pocketful of Sugar

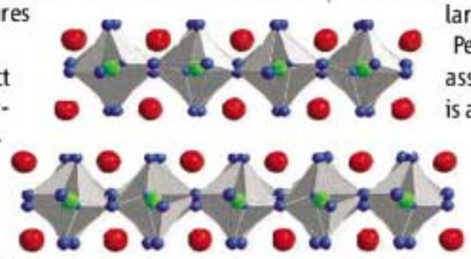
Selective binding of distinct sugars in water is a challenge for molecular recognition because the abundant OH substituents must be differentiated from one another, as well as from the markedly similar surrounding solvent. **Ferrand *et al.*** (p. 619) have prepared an organic receptor that achieves the task for certain disaccharides with an efficacy approaching that of the much more structurally complex lectin proteins, and so holds promise for biochemical applications. The receptor binds cellobiose and related compounds, in which all OH groups are equatorially oriented, with an association constant of ~600 inverse molar; the affinity drops more than 10-fold for substrates with an axial OH group. Nuclear magnetic resonance spectroscopy confirms a binding motif in which polar walls in the receptor interact favorably with the hydroxyls while aromatics at the top and bottom straddle the alkyl portions of the guest.

Mapping Mantle Heterogeneity

Earth's upper mantle shows a series of seismic discontinuities that have been linked to phase changes in mineralogy. Although the discontinuities occur at similar depths, there are local variations. **Schmerr and Garnero** (p. 623) investigate mantle structures beneath South America and adjacent oceans by stacking up weak precursors to *SS* seismic waves to map the discontinuities at depths of approximately 410- and 660-kilometers (km). On the downdip side of subduction zones, they see that the 410-km discontinuity occurs tens of kilometers deeper, counter to expectations for cold slab material. Explaining the features seen requires both chemical and thermal contributions to the phase changes and confirms the influence of deep tectonic processes in generating mantle heterogeneity.

A Stress on the Insulating Phase

The band theory for conductivity of solids predicts that materials with an odd number of electrons in their unit cell would behave as metals, but some materials, such as NiO, are insulators at low temperatures because of the dominating effect of Coulomb interactions and electronic correlations. These insulators can undergo a transition to a metallic phase (by increasing temperature), but typically these metal-to-insulator transitions (MITs) are accompanied by structural phase transitions. **Moore *et al.*** (p. 615) show that in the layered perovskite $Ca_{1.9}Sr_{0.1}RuO_4$, the surface undergoes its MIT at 130 Kelvin, well below the bulk transition temperature of 154 Kelvin that is accompanied by a structural phase transition. The authors argue that surface stresses that allow that Ca and Sr ions to be pulled into the bulk stabilize a surface phase that favors the Mott insulator ground state relative to the bulk structure. Thus, the MIT can occur before the phase transition.



Inevitable Uncertainty

Climate sensitivity is defined by the change in global average temperature that would result from changes in radiative forcing equal to that which would be caused by a doubling from preindustrial levels of the atmospheric concentration of CO_2. Past work has shown that while the most likely value of climate sensitivity is between 2.0° and 4.5°C, there is a small probability that the increase could be much higher—8°C or even more. This persistent, high-temperature tail of low probability has been one impediment to political action, as policy-makers have been reluctant to formulate policies to address climate change when the range of uncertainty is so large. **Roe and Baker** (p. 629; see the Perspective by **Allen and Frame**) assert that this tail of low probability is an intrinsic feature of the climate system, not a result of inadequate data or models, and that this tail will persist even in the face of more observations and more advanced modeling. They conclude that putting off decisions about climate policy until greater certainty is achieved is futile.

Thawing and Warming

Around 18,000 years ago, near the beginning of the last deglaciation, the atmospheric concentration of the greenhouse gas methane began to rise rapidly, but the origin of this increase is still uncertain. **Walter *et al.*** (p. 633) add another potential methane source to the mix: the frozen areas of northern Asia and North America that were not covered by ice sheets. As the climate

Continued on page 531

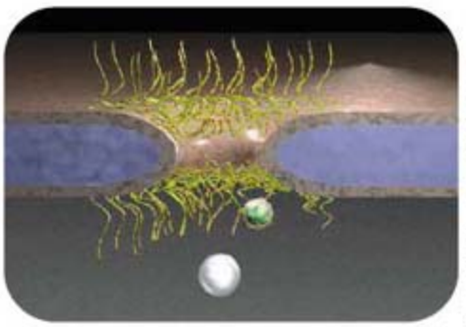
CREDITS (TOP TO BOTTOM): ANDRE KESSLER/CORNELL UNIVERSITY; MOORE *ET AL.*

Continued from page 529

began to warm, these grounds thawed and lakes formed that would have emitted large volumes of methane bubbling up from their organic-rich sediments. Such a process could have supplied as much as 85% of the methane that Arctic and boreal regions are understood to have contributed during deglaciation. This methane emission would have contributed significantly to the warming that occurred at the Pleistocene-Holocene transition.

Pack Mentality?

Explaining the origin of altruism and parochialism has posed a challenge for theoretical biologists. **Choi and Bowles** (p. 636; see the Perspective by **Arrow**) describe a simulation based on interactions between groups in a game-theory framework in which hostile intergroup interactions lead to war and nonhostile interactions lead to trade. Groups composed of individuals who are both altruistic and parochial—who favor members of their own group and disfavor outsiders—are more successful than groups that are either only altruistic or only parochial.



CREDIT: HANS-RUDOLF HEBER/UNIVERSITY OF BASEL, SWITZERLAND

Regulating Nuclear Transport

In eukaryotic cells, the nuclear pore complex (NPC) acts selectively to gate entry and exit of macromolecules into and out of the nucleus. **Lim *et al.*** (p. 640; published online 4 October) studied the biophysical response of the phenylalanine-glycine (FG)–domain of one of the nuclear pore proteins to biochemical interactions that govern nucleocytoplasmic transport. The FG-domains collapse into more compact structures upon binding to the nuclear transport receptor karyopherin-β. This collapse is reversed by Ran guanosine triphosphate, a known regulator of nuclear transport. The reversible collapse of the FG-domains may represent the underlying mechanism that regulates passage through the NPC.

Plant-Pathogen Arms Race

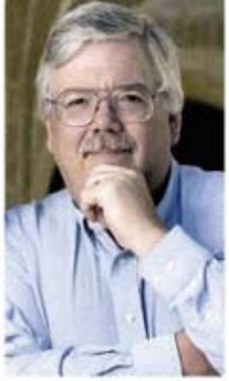
Plants recognize pathogens through immune-like receptors, which activate a resistance response. In turn, pathogens have evolved means to modify plant signaling pathways to avoid triggering the resistance response. **Kay *et al.*** (p. 648) and **Römer *et al.*** (p. 645) tackle the molecular mechanisms underlying this evolutionary arms race between plants and pathogens. The bacterial type III effector protein, AvrBs3, functions as a pathogenicity factor in susceptible host plants, which lack a resistance gene known as *Bs3*, by acting as a transcriptional activator. In contrast, plants carrying Bs3 recognize the AvrBs3 protein and activate the resistance gene *Bs3*, which simulates the plant resistance pathway.

Extracellular Death Factor

Programmed cell death (PCD) has traditionally been considered to be restricted to eukaryotic multicellular organisms; however, several genetic modules in prokaryotes are known to mediate a type of programmed cell death. In *Escherichia coli*, *mazF* encodes a stable toxin, and *mazE* encodes a labile antitoxin, that prevents the lethal effect of MazF. **Kolodkin-Gal *et al.*** (p. 652; see the Perspective by **Kolter**) now show that *E. coli mazEF*–mediated cell death is a population phenomenon that requires a quorum-sensing signal molecule, extracellular death factor (EDF). EDF is a symmetric, linear pentapeptide whose amino acid sequence is Asn-Asn-Trp-Asn-Asn. In synthetic peptides, the symmetrical arrangement of each of the five amino acids of EDF was important for *mazEF*-mediated killing activity.

Drug Craving, Malaise, and the Insula

An important factor that contributes to drug-seeking in addicted individuals is the negative feelings that result from abstinence. Such mood states are monitored by the interoceptive sensory system, and particularly by a brain area called the insular cortex, known to process emotional information. **Contreras *et al.*** (p. 655) observed that inactivation of the rat posterior granular insula reversibly disrupts the craving for amphetamine in animals repeatedly injected with amphetamine, as well as the behavioral signs of malaise induced by lithium administration. Thus, therapeutic interventions in the insula may help to alleviate drug cravings.



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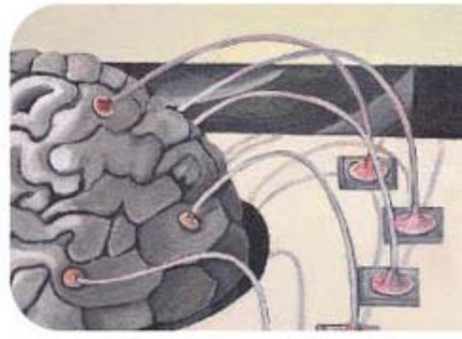
On Neuroethics

HUMAN SOCIETY IS THE SOCIETY OF HUMAN BRAINS. OF COURSE THOSE BRAINS ARE encased in, affected by, and dependent on the rest of the body, but our most important interactions are with other people's brains, as manifested through their bodies. On 3 November 2007, the Society for Neuroscience begins its 37th annual meeting. Since 1970, the event has grown into one of the world's largest scientific meetings, drawing more than 30,000 scientists to discuss brains. This surge in attendance comes from an explosion in knowledge: We know almost infinitely more than we did 37 years ago, even though we still understand little.

Our new knowledge has begun to spill out from the laboratory into society as neuroscience raises new ethical, legal, and social concerns. Some, using journalist William Safire's term, talk of "neuroethics." Others reject that term or question whether it really is a new area. But that is less important than the real questions being raised. Some of those questions entail the ethics of conducting neuroscience research. The brains of "normal" people in some imaging studies yield clinically significant findings disconcertingly often: 8 to 10% of the time in some studies. What kind of information and follow-up do we owe those people? Other studies may have military implications: Suppose brain stimulation created an indefinitely awake and alert soldier or pilot? Will neuroscience be a new source of dual-use technologies such as those we worry about for biological or chemical warfare? Other researchers are studying "the neuroscience of ethics," as philosophers and neuroscientists explore how brains make decisions when confronted with moral dilemmas. The implications are unclear, but the work is fascinating.



For me, the most exciting questions involve how neuroscience might change society. If we could reliably predict that certain adolescents will eventually be diagnosed with schizophrenia, what use should we make of that information? If learning how brains make decisions could reliably indicate malign intent, should we use that information in criminal decision-making? What if we produce a pill that enables people in early stages of dementia to make, retain, and retrieve declarative memories? Should it be used by healthy people, such as premedical students?

Alas, some of this is not speculation. Already, at least one company is selling functional magnetic resonance imaging services for lie detection. Some foreign hospitals are performing psychosurgery for drug addiction. And judges and juries are being asked to make decisions based on beautiful "pictures" of people's brains. People working in neuroethics need both to point out when unproven new technologies are being used recklessly and to explore the social consequences of effective new technologies. In both cases, we need to maximize the benefits of the applications of neuroscience and minimize their harms.

Some good things are happening along this line. The Neuroethics Society was founded last year to promote the study of these issues. The Dana Foundation has been supporting these efforts for several years, often with the American Association for the Advancement of Science; and in October 2007, the MacArthur Foundation announced a major project on Neuroscience and Law to fund research in these intersecting disciplines. Through these efforts and independently, professors of law, education, business, and philosophy are coming together with neuroscientists, psychologists, neurosurgeons, and psychiatrists to discuss the implications for society of this expanding science of the brain.

But more needs to be done. The U.S. Human Genome Project had a program for studying the ethical, legal, and social implications (ELSI) of genetics, but no similar program exists for neuroscience, although we are our brains far more truly than we are our genomes. The ELSI program may not be the right model, but funds are essential to promote this kind of research, particularly by medical school researchers who depend on grants. In these days of tight federal budgets, money is hard to get. But to fund science without supporting work on its social consequences will ensure that the neuroscience revolution brings far too much social pain and chaos along with its scientific and medical breakthroughs.

– Henry Greely

10.1126/science.1150557

Magellanic Cloud.

ASTROPHYSICS

Brief Encounter

The Small and Large Magellanic Clouds are our nearest galactic neighbors, visible in southern skies as thumb-sized smudges on the sky. Recent tracking with the Hubble Space Telescope showed that they are circling the Milky Way faster than was once thought, closely approaching the Milky Way's escape velocity. Besla *et al.* model the past motions of the Magellanic Clouds using the updated speeds and latest cosmological parameters and find that they are probably interlopers on their first pass of the Milky Way, rather than long-term companions on continuous orbits. This brief encounter scenario resolves some questions but raises others. It may explain why there has been an upsurge in star formation in the Clouds within the past few billion years. However, it also means that the Clouds may have had less of an effect on the diffuse hydrogen envelope of the Milky Way than had been assumed, as they have not been around long enough to warp the edges of the pancake of hydrogen in which the Milky Way sits or to pull out the Magellanic Stream, a band of hydrogen gas that almost circles the Milky Way and seems to follow the Clouds. — JB

Astrophys. J. **668**, 949 (2007).

CREDITS (TOP TO BOTTOM): NASA, ESA, AND THE HUBBLE HERITAGE TEAM; ADAPTED FROM FILIPPELLI *ET AL.*, *DEEP-SEA RESEARCH II* 10.1016/J.DSR2.2007.07.021 (2007)

MATERIALS SCIENCE

A Measured Flow

Measurement of the flow of thin films is complicated by the coupling of frictional forces and the driving force (pressure) at the molecular level. To this end, Xu *et al.* designed a set of brushlike polymers, with a flexible backbone connected to a dense shell of rigid side chains. When the polymers are driven across a substrate, the reduced interaction of side groups with the substrate causes the backbone to coil, and the extent of this compacting can be used to gauge local variations in film pressure. Conformational changes can also reveal the friction coefficient at the substrate. The authors tracked polymer spreading on mica or graphite using atomic force microscopy (AFM) to probe the local chain conformations. The friction coefficient showed strong humidity dependence on the hydrophilic mica substrate, though not on hydrophobic graphite. The limitations of AFM detection notwithstanding, the authors envision a range of situations where these polymer probes could be useful pressure sensors. — MSL

Adv. Mater. **19**, 2930 (2007).

OCEAN SCIENCE

Down from the Shelves

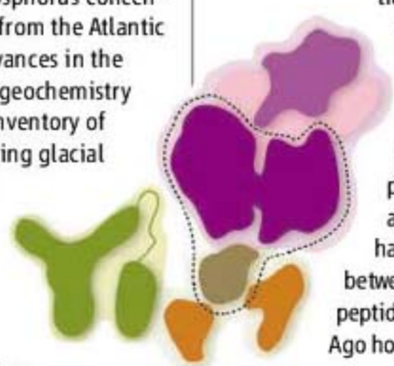
Biological productivity in the ocean—which helps control climate on glacial time scales through its effect on the global carbon cycle—is regulated by the availability of nutrients such as phosphorus. The marine phosphorus cycle has in turn been thought to depend greatly on the variations in sea level caused by the growth and decay of continental ice sheets during the glacial cycle, which alternately expose and submerge continental shelves, but data relating to this hypothesis are scarce. Filippelli *et al.* combine measurements of the phosphorus concentration in deep sea sediments from the Atlantic and the Pacific with recent advances in the understanding of phosphorus geochemistry to show that the phosphorus inventory of those sediments increased during glacial periods and decreased during interglacials over the past 400,000 years. This finding supports the Shelf-Nutrient Hypothesis, which postulates that phosphorus should be transferred from shallow continental margins to the deep sea when continental shelves become exposed during glacial sea-level lowstands. These results should help to define the role that productivity plays in the regulation of atmospheric carbon dioxide over glacial/interglacial transitions, as well as the respective roles of external processes such as dust deposition, and internal processes such as upwelling, in the regulation and distribution of ocean nutrients. — HJS

Deep-Sea Res. II 10.1016/j.dsr2.2007.07.021 (2007).

MOLECULAR BIOLOGY

Hooked on Interference

Argonaute (Ago) proteins are the effectors that lie at the heart of RNA interference. They bind small interfering (si) or micro (mi) RNAs and use them to target and to repress (in most cases) complementary RNAs, either directly, at the posttranscriptional stage, or indirectly (in the case of some siRNAs) at the transcriptional stage. In fission yeast, transcriptional gene silencing (TGS) is mediated by the RITS complex, which includes the Ago1 and Tas3 proteins. Till *et al.* have dissected the interaction between Tas3 and Ago1 and find a peptide motif, which they call the Ago hook, in Tas3 that interacts both in vitro and in vivo with the PIWI domain in Ago1. The hook binds in a conserved pocket within the Ago PIWI domain; this same pocket binds the 5′ end of the siRNA/miRNA guide strand. The hook is required for TGS in vivo in fission yeast and can block *Drosophila* miRNA-mediated repression in vitro. Furthermore, a human Ago-interacting protein harbors a motif that is similar in sequence and in function. The hook is likely to be pivotal in recruit-



The hook/PIWI interaction (outlined in black) within the RITS complex.

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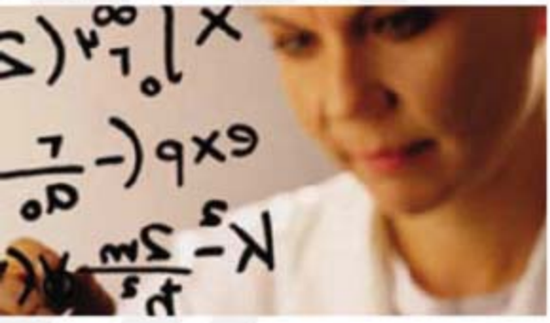

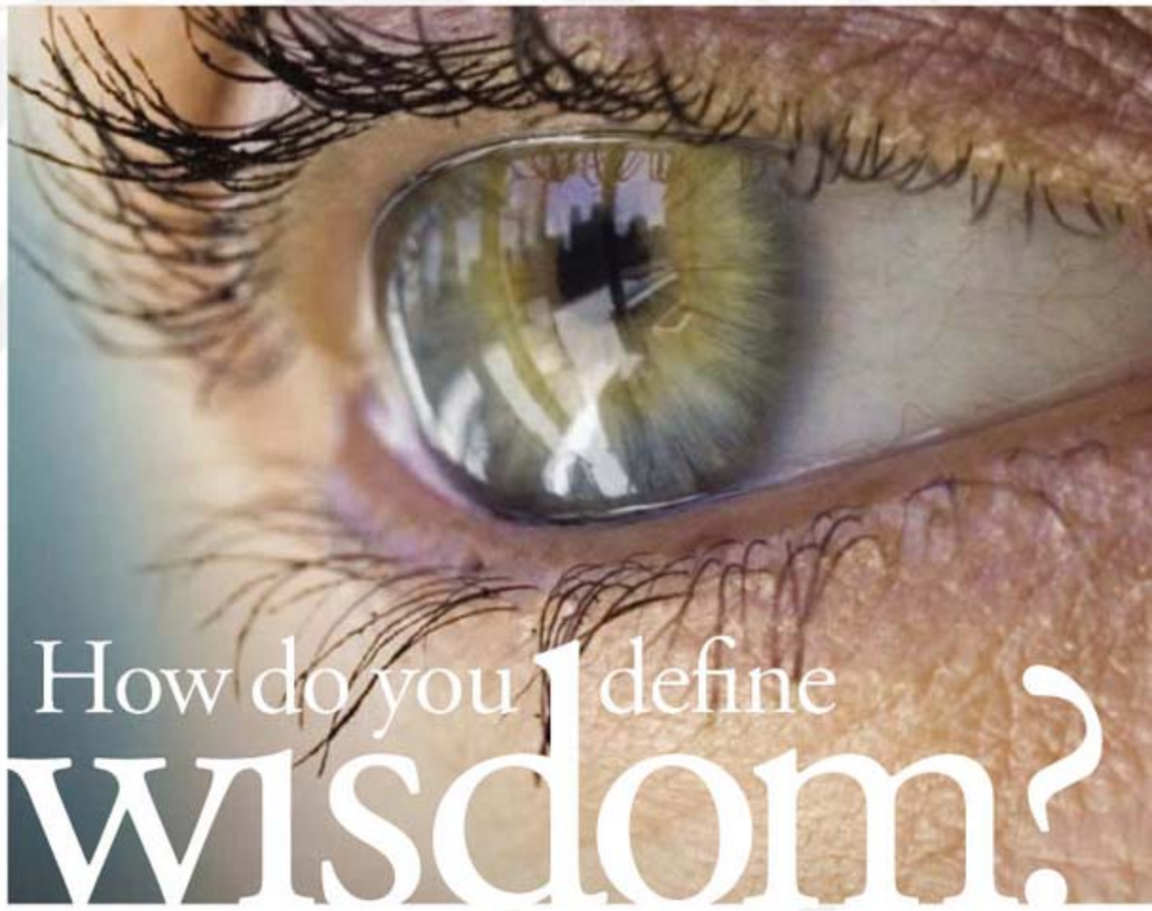

How do you define wisdom?

DEFINING WISDOM

A PROJECT OF THE UNIVERSITY OF CHICAGO

THE WISDOM PROJECT

The Arete Initiative at the University of Chicago is pleased to announce a new $2 million research program on the nature and benefits of Wisdom. Although it has been neglected in the past, a new scientific and scholarly study of Wisdom has the potential to raise new questions, challenge assumptions, and develop new theoretical and empirical models which will enliven debate within and across disciplines. In this new grant competition, we seek to support highly original, methodologically rigorous projects from a broad range of disciplines on the theme of 'Defining Wisdom.'

2008 RESEARCH GRANTS

In 2008, up to twenty (20), two-year research grants will be awarded to scholars from institutions around the world who have received their Ph.D. within the past ten years. For a description of the required letter of intent and more information about the Wisdom Project, go to: www.wisdomresearch.org or contact us directly at wisdom@uchicago.edu.

Letter of Intent Deadline: November 19, 2007.

ARETE INITIATIVE

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AREAS

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ing Ago proteins to specific subcellular locations and in influencing the binding of siRNAs and miRNAs, and thus may determine the functional output of the various Ago complexes. — GR

Nat. Struct. Mol. Biol. **14**, 897 (2007).

MICROBIOLOGY

It's a Jungle Down Here

Analyzing DNA sequences in unpurified or partially fractionated samples (such as a drop of water from the Sargasso Sea or from an acid mine drain) has proven to be remarkably informative. A high degree of organismal diversity has been documented, and extending this approach to terrestrial

systems has uncovered previously unsuspected and intermingled communities of bacteria, archaea, and fungi. Vandenkoornhuyse *et al.* have begun to look at the exchange of goods in one such marketplace by exposing pieces of turf from UK grassland (Scotland) or from French peatland (Normandy) to $^{13}CO_2$ and following the transfer of the isotope into ribosomal RNA of microbes associated with the plant roots. Interpreting measurements of a nonstationary process can be somewhat challenging, but a first glance reveals a broader-than-expected population diversity and a marked unevenness in the rate of primary consumption—that is, the uptake of photosynthetic products by the root-dwelling bacteria and fungi. — GJC

Proc. Natl. Acad. Sci. U.S.A. **104**, 16970 (2007).

IMMUNOLOGY

Rules of Regulation

What overarching factors regulate the regulatory T (T_{reg}) cells that guide our immune systems to fight infectious diseases while leaving ourselves unharmed? By scrutinizing molecular events inside T_{reg} cells, Tao *et al.* implicate the activity of chromatin remodeling proteins. Initial evidence emerged from the observation that a histone deacetylase (HDAC) inhibitor increased the level of the chief transcription factor in T_{reg} cells, Foxp3, as well as the number and activity of T_{reg} cells in mice. Furthermore, in culture-stimulated T_{reg} cells, HDAC9 was the most prominently expressed member of the deacetylase family, and T_{reg} cell function was enhanced in its absence. Acetylation of the Foxp3 protein itself was also observed and corresponded with an increase in Foxp3 binding to its target genes. Finally, HDAC inhibition helped curtail inflammatory T cell responses, both to transplanted grafts and in a model of inflammatory bowel disease. The finding that regulating acetylation/deacetylation has such a measurable influence on T_{reg} function and that it operates at the level of both the *Foxp3* locus and the transcription factor suggests that different avenues might be open for testing HDAC inhibition as a form of immunotherapy. — SJS

Nat. Med. **13**, 10.1038/nm1652 (2007).

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<< An Endogenous SERM?

Although estrogens had long been thought to protect against cardiovascular disease, this assumption has been challenged by the results of clinical trials that failed to corroborate protective effects of hormone replacement therapy in postmenopausal women. Umetani *et al.* found that the cholesterol metabolite 27-hydroxycholesterol (27HC, which is found in atherosclerotic lesions) competed with estradiol for binding to estrogen receptors α and β (ERα and ERβ), inhibited estradiol-dependent activation of transcriptional activity of the receptors, and inhibited the estradiol-dependent association of ERβ with the transcriptional coactivator SRC-1. In mice fed a diet rich in cholesterol and fat, hypercholesterolemia was associated with increased vascular concentrations of 27HC, comparable to those affecting ER function; 27HC also inhibited the estradiol-dependent increase in inducible and endothelial nitric oxide synthase (iNOS and eNOS) expression in mouse aortic cultures. Administration of 27HC decreased aortic expression of iNOS and eNOS in vivo, and dietary hypercholesterolemia was associated with a decrease in iNOS mRNA and protein in male mice. The pro- or anti-estrogenic effects of 27HC depended on tissue type, leading the authors to propose that it may act as an endogenous selective estrogen response modulator (SERM). The anti-estrogenic effects of 27HC in the vasculature led them to suggest that it might contribute to a lack of cardioprotective effects of estrogen in postmenopausal women. — EMA

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CREDIT: A. HEINEMEYER, CENTRE FOR TERRESTRIAL CARBON DYNAMICS, YORK, UK.

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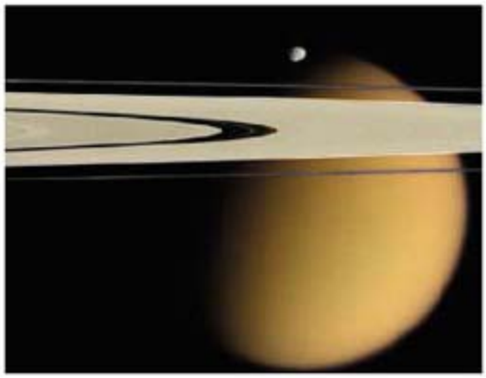
Mooning About: Cassini Turns 10

NASA's Cassini mission celebrated its tenth year last week by releasing images of the solar system's preening beauty, Saturn, and its fawning entourage of moons and rings. Eagle-eyed researchers spotted "moonlets" plowing through the delicate rings and reported the results in this week's issue of *Nature*.

The moonlets measure just 30 to 70 meters across, but most of the debris in the rings measures less than 10 meters, so the moonlets leave a traceable wake. Saturn's rings vary in thickness from about 100 meters to slightly more than 1 km.



In the image, Epimetheus (116 km across) floats just above Titan (5150 km), the largest of Saturn's moons. The light-colored streaks in the ring may be caused by moonlets. The dark-colored section in the middle of the ring is the 325-km-wide Encke gap, probably caused by a gravitational resonance.

Cassini has mapped 60% of Titan's northern hemisphere, which is home to lakes, rivers, and seas of liquid methane and ethane. The southern half is slated to be mapped next.

CREDITS (TOP TO BOTTOM): COURTESY OF TERRY DAVIS; NASA/JPL/SPACE SCIENCE INSTITUTE; HARVARD NEWS OFFICE

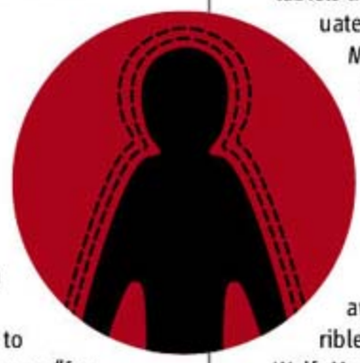
Golden Oldies

NET WATCH

Spending your working hours pondering how our bodies break down as we get older might sound a little depressing. But research on aging is booming, and the field's good health is on display at the blog Ouroboros, which is named for a symbol of endlessness. Three postdocs from leading aging research labs offer their takes on the latest results from conferences and the literature. In a little more than a year, the authors have touched on topics as diverse as the evolution of whale menopause, cell death during muscle aging, and a potential new blood test for Alzheimer's disease. The site is aimed at researchers, but it can also help beginners get up to speed. >>
ouroboros.wordpress.com

Prescription Hazards

"Don't touch this stuff."
"Take anywhere."
"Chills or shaking."
"Having an experience with God."



What is the meaning of this icon? In an outpatient clinic survey, researchers showed common prescription labels to 253 patients and asked, "What does this mean to you?" For this icon—which means "for external use only"—46% came up with answers such as those above.

Inscrutable, inconsistent drug labeling was the topic of a meeting this month at the Institute of Medicine in Washington, D.C. "Nobody regulates warning labels," says Terry Davis, a professor of medicine at the Louisiana State University Health Sciences Center in Shreveport, who conducted the survey. Nor is there any standard terminology for directing patients on how to use their prescribed medications. Even instructions as simple as "take two tablets twice daily" will stump college graduates, says health services researcher Michael Wolf of Northwestern University in Evanston, Illinois. With the average American over 65 taking eight kinds of medications and ordering 27 refills a year, the possibilities for misunderstandings are legion.

"It's amazing we've gotten away with presenting the most horrible information for so long," says Wolf. Meeting attendees agreed that standardization is long overdue but said voluntary efforts would be preferable to more regulations. Target is one store chain that is taking action, with "ClearRX," a pill bottle storable on its top with a wraparound bottom and flat front offering more surface area for explicit instructions.

New Value in Old Casts

Plaster reproductions of Maya and Aztec carvings, which have languished for a century in storage at Harvard University's Peabody Museum, are attracting new interest from scholars now that many of the originals have been eroded or destroyed.

Curators, students, and conservationists are pitching in with vacuums, brushes, and dry sponges in a 5-month project to clean and catalog 650 casts for study. Some of the molded copies are up to 2 meters tall and weigh almost 230 kilograms. Made by Harvard scholars in the 1890s, they reproduce hieroglyphs from 25 archaeological sites in Mexico, Guatemala, and Honduras, as well as images of rulers and rituals. They were used in exhibitions, such as the World's Columbian Exposition of 1893 in Chicago, and later stashed away.

"For a long time, nobody thought that they were important because they weren't the originals and were placed in less-than-optimal conditions," says museum spokesperson Pamela Gerardi. Now, however, the original monuments have eroded from rain and tropical heat; some have been stolen or smashed up to construct walls.

EDITED BY YUDHIJIT BHATTACHARJEE

POINT ↔ COUNTERPOINT

Although scientific links between India and the United States have strengthened in recent years, each country has its own agenda in space exploration. In separate interviews recently, *Science* asked **Michael Griffin**, NASA's administrator, and **G. Madhavan Nair**, chair of the Indian Space Research Organisation (ISRO), about Indo-U.S. collaboration.

Q: Are India and America racing to get a person once again on the moon?

Griffin: Certainly we are not racing; we can hope to go together. NASA will not join the Indian program but would want India to join with us.

Nair: The relationship between ISRO and NASA has improved, [and] there is a desire to cooperate.

Q: Will NASA train Indian astronauts for the space shuttle and beyond?

Griffin: We did make the offer, and the Indian government declined. Maybe at a later time when we are flying beyond the space shuttle, India may choose to join in.

Nair: As yet, the plans are independent of each other. If there is an immediate need to send an Indian astronaut, there are the Russian modules. But India's access to space is important.

Q: Are U.S. export-control laws a stumbling block?

Griffin: There is some concern and frustration in India with [these laws], and it is frustrating for us as well. … We are very concerned about the proliferation of missile technology.

Nair: Thanks to the export-control laws, ISRO has learnt [to indigenize technology] the hard way. Removal of these restrictions would speed up India's efforts to undertake a manned space mission.

CREDITS (CLOCKWISE FROM TOP): NASA/RENEE BOUCHARD; PALLAVA BAGLA; NSF/THEREVID PEET PROJECT; GE; NASA

IN THE COURTS

FORTUNE LOST? Entomologist Evert Schlinger has studied spiders and flies for 7 decades. He also oversaw a family foundation once worth nearly $55 million that supported researchers around the country. Somehow, it all went bad.

In 2004, Schlinger resigned under pressure from the foundation, which sued him and several advisers for fraud and mismanagement. Last month, a jury in Santa Barbara County, California, found Schlinger and the others guilty of those charges and ruled that they owed the foundation $35 million. The foundation's lawyer, Scott Campbell, argued that Schlinger had embezzled $293,760 and illegally invested more than $20 million in a failing go-cart company.

Schlinger denies any theft. He admits he and his advisers "made some mistakes now and then" but says the goal was to prevent taxes from eroding the foundation's endowment. Campbell says the foundation, now worth about $6 million, will try to recoup its losses. "The real tragedy here is the science," he says. "Entomology is what suffers."

AWARDS

COMPUTE THIS. An Italian physicist is the winner of this year's $350,000 Microsoft European Science Award, given out by the United Kingdom's Royal Society and the French Académie des Sciences. Giorgio Parisi, a professor of quantum theories at the University of Rome "La Sapienza," received the honor last week for his contributions to particle physics, quantum field theory, and statistical mechanics. Parisi gets to keep $10,000 for himself; he'll use the rest of the award to build a next-generation computing platform capable of simulating complex systems.

IN MEMORIAM

UNDYING SPIRIT. The General Electric Co. (GE) has donated $300,000 to endow three graduate fellowships at Virginia Polytechnic Institute and State University (VT) in Blacksburg in honor of Liviu Librescu, Kevin Granata, and G. V. Loganathan, engineering professors killed on campus earlier this year by a student gunman (*Science*, 27 April, p. 525).

"We hope in some small way we can contribute to the healing process," says Charles "Chip" Blakenship Jr., general manager of the GE Aero Energy group. As head of recruiting for GE at the university, Blakenship estimates that he hires 50 to 70 Hokies (VT alums) a year. "It hit me very hard," Blakenship says of the tragedy. "I'm a second-generation Hokie."

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U.K. university in antiquities flap 554

GENETICS

Ancient DNA Reveals Neandertals With Red Hair, Fair Complexions

What would it have been like to meet a Neandertal? Researchers have hypothesized answers for decades, seeking to put flesh on ancient bones. But fossils are silent on many traits, from hair and skin color to speech and personality.

Personality will have to wait, but in a paper published online in *Science* this week (www.sciencemag.org/cgi/content/abstract/1147417), an international team announces that it has extracted a pigmentation gene, *mc1r*, from the bones of two Neandertals. The researchers conclude that at least some Neandertals had pale skin and red hair, similar to some of the *Homo sapiens* who today inhabit their European homeland. The paper comes on the heels of one that used similar techniques to show that Neandertals shared the modern human form of the only gene so far known to influence human speech, *FOXP2*. Although researchers are working to sequence the entire Neandertal genome (*Science*, 17 November 2006, p. 1068), these are the first specific nuclear genes to be retrieved. "These are the two genes you'd most like to see from a Neandertal," explains Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, who led the *FOXP2* study.

The *mc1r* paper is "logical, elegant, and convincing," says anthropologist Nina Jablonski of Pennsylvania State University in University Park. "It's a great paper," agrees molecular geneticist and pigmentation expert Rick Sturm of the University of Queensland in St. Lucia, Australia.

Many of the Neandertals cavorting in museum dioramas around the world already have pale skin or red hair, because anthropologists have long predicted this coloration on the basis of evolutionary theory. The dark skin beneficial in Africa offers no advantage at high latitudes, and in cloudy Europe, pale skin facilitates vitamin D production, Jablonski says. But there was no proof of Neandertals' looks until a team led by Carles Lalueza-Fox of the University of Barcelona in Spain and Holger Römpler of the University of Leipzig in Germany set out to retrieve the *mc1r* gene from a 43,000-year-old Neandertal from El Sidrón, Spain, and a 50,000-year-old specimen from Monti Lessini, Italy.

MC1R is a cell membrane receptor that helps regulate the balance between red-and-yellow-colored pheomelanin and black-and-brown-colored eumelanin. Living people with variations that make the receptor work poorly tend to have red hair and pale skin, although other pigmentation genes also have strong effects (*Science*, 2 March, p. 1215).

Using the polymerase chain reaction (PCR) to target and amplify the gene, the researchers found a point mutation not seen in living humans. They checked about 3700 people, including everyone involved in the project, to be sure that the variant was unique to Neandertals. Next, they explored the variant's function by expressing it in human cells and found that it impaired the receptor's activity. "If you have a variant with this low action in modern humans, you get classically Irish-looking red hair and pale skin" in homozygotes, people with two copies of the variant, says team member Michael Hofreiter of the Max Planck Institute in Leipzig. The researchers calculate that at least 1 in 100 Neandertals would have been homozygotes. Thus Neandertals and *Homo sapiens* in Europe followed independent evolutionary paths to a similar phenotype, Lalueza-Fox says.

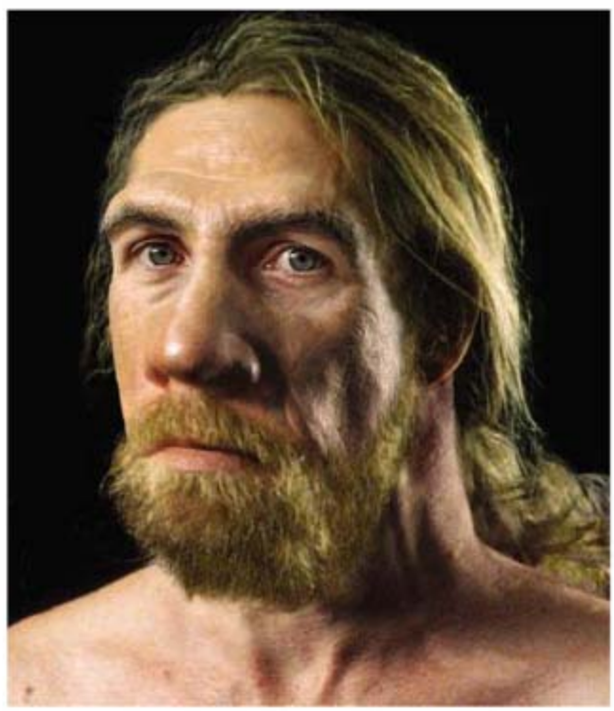
"I'm convinced that what they're saying is real," says Sturm, who has used similar functional assays to check *mc1r* variants in living people. Lalueza-Fox adds that Neandertals may have carried a variety of changes in *mc1r*, as we do, and so may have had a spectrum of skin and hair colors.

Pääbo and colleagues also used targeted PCR to isolate the *FOXP2* gene. They chose *FOXP2* because people with mutations in the gene have impaired speech. Pääbo's team had previously traced the gene in living people and suggested that the unique human variant was selected relatively recently, less than 200,000 years ago—long after Neandertals and modern humans had diverged (*Science*, 16 August 2002, p. 1105). The implication was that Neandertals lacked the modern human form, Pääbo says.

But to their surprise, that's not what they found when they sequenced the gene from two bones from El Sidrón, where Lalueza-Fox runs a "clean" excavation for DNA analysis. Both bones carried the modern human version of *FOXP2*. That doesn't necessarily mean Neandertals spoke as we do, because many genes presumably influence speech. But "from the point of view of the one gene we know, there's nothing to say that Neandertals were different from us" in their language abilities, Pääbo says.

Because the Neandertal *FOXP2* gene matched that found in living people, Pääbo's team used extra controls to try to rule out contamination with modern human DNA. For example, they sequenced the Neandertal Y chromosome and found that it differed from that of living men at five key sites. No contamination of the Y chromosome strengthens the case that the *FOXP2* result is real, Pääbo says.

The Y chromosome finding also argues ▶



Ginger man. Some Neandertals had red hair and pale skin, as seen in this reconstruction of a French fossil.

CREDIT: RECONSTRUCTIONS AND PHOTOGRAPHY BY JOHN GURCHE

against interbreeding between Neandertals and the modern humans then entering Europe. "I find it paradoxical in some ways," says Lalueza-Fox, who is an author of both studies. "The papers make Neandertals more like modern Europeans, with light skin and hair color and language abilities, and yet there are no signs of interbreeding with modern humans."

But others aren't yet ready to concede that either contamination or mixing has been completely ruled out. "The additional controls give one more confidence that contamination is not a problem, but we can't be 100% sure," says evolutionary geneticist Jeff Wall of the University of California, San Francisco, who in August reported what he saw as contamination in Pääbo's group's bulk Neandertal sequencing (*Science*NOW, 29 August, sciencenow.sciencemag.org/cgi/content/full/2007/829/4).

Wall adds that if the *FOXP2* result is real, it's possible that Neandertals acquired the human *FOXP2* variant by mixing. "If there was admixture, it wasn't very much. But we can't tell if there was a small amount." Pääbo says he can't rule out that scenario but considers it "unlikely," given the genetic data so far.

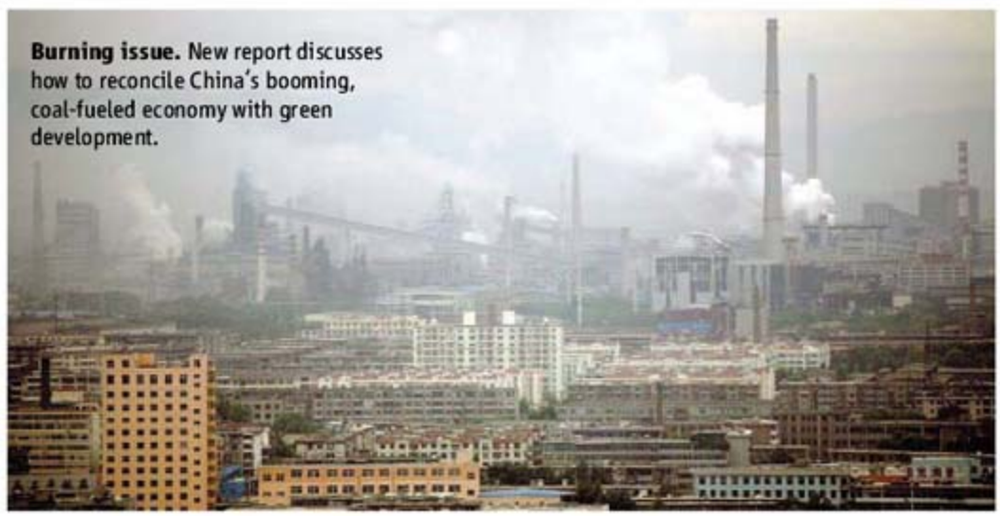
–ELIZABETH CULOTTA

ENERGY POLICY

National Academies Make Case for Sustainable Growth

Use energy more efficiently. Put a price on carbon emissions. Develop green energy sources.

Those recommendations on sustainable development, from a report released this week by dozens of the world's national science academies, may be familiar. But the scientists behind the 174-page effort believe that the urgency of the problem will make up for its lack of originality in grabbing the attention of policymakers around the globe, and they intend to launch a major effort to get the message out. "The goal is to work fairly deeply into governments," says Hal Harvey of the Menlo Park, California–based William and Flora Hewlett Foundation, which helped fund the report, dubbed *Lighting the Way*.



Burning issue. New report discusses how to reconcile China's booming, coal-fueled economy with green development.

CREDIT: NATALIE BEHRING/BLOOMBERG NEWS/LANDOV

The peer-reviewed report's recommendations reflect the diverse perspective of the 15 experts, nominated from more than 90 national academies, working under the auspices of the 7-year-old InterAcademy Council (IAC) in Amsterdam, the Netherlands. "Meeting the basic energy needs of the poorest people on this planet is a moral and social imperative" that technology transfer and international efforts could address, the report begins. On energy efficiency, it recognizes that most building construction will occur in cities of the developing world, and it calls on local governments and scientists to develop sustainable practices. California and Brazil are held up as models for energy efficiency and the use of biofuels. Report co-chair and director of Lawrence Berkeley National Laboratory Steven Chu calls the "international flavor" of the 2-year effort unique, noting that its proposed doubling of applied energy research says that the money must be "internationally coordinated."

Co-chair José Goldemberg, secretary for the environment in São Paulo, Brazil, believes that governments are eager to hear those messages, and he notes that many national academies in the developing world already "have close ties to governments." The report, requested by the science academies of Brazil and China, was rolled out this week with a workshop in Beijing and with plans for a follow-up symposium in Brazil. The Chinese Academy of Sciences brokered a meeting between Chu and Chinese Premier Wen Jiabao, and CAS President Lu Yongxiang announced plans, including the creation of a renewable energy R&D center, to help wean China from its heavy dependence on coal. A major element, Lu says, will be a rapid expansion of China's nuclear industry, which currently generates just 1.6% of the nation's power supply.

The report's emphasis on the developing world should be popular in Washington, D.C., predicts Paul Bledsoe of the nonprofit National Commission on Energy Policy. Although Bledsoe believes that "speedy U.S. action is a necessary precursor" to sustainable policies in the developing world, he notes that the willingness of developing nations to tackle the problem has been "the sticking point [in Washington] all along." Roughly one-fourth of the $550,000 the Hewlett Foundation spent on the report is devoted to an international media push that would bolster outreach by individual academies.

Chu hopes the new report will make a bigger splash than other academic efforts; previous IAC reports on women in science and African agriculture, for example, have caused barely a ripple. His model is the 2005 U.S. National Academies' report on U.S. science priorities, *Rising Above the Gathering Storm*, that served as the basis for the America COMPETES Act, which became law this summer. "We didn't make claims for originality," says Chu, a member of that panel, too. "[But] that report was incredibly successful."

–ELI KINTISCH

With reporting by Richard Stone in Beijing.

NUCLEAR PHYSICS

Neutron-Laden Nucleus Pushes Limit

Nuclear physicists are striving to find out how many neutrons can be packed into a nucleus. But a newly discovered nucleus suggests that the limit may be higher than theorists had thought—perhaps too high for experimenters to reach.

The new nucleus, aluminum-42, contains 13 protons and 29 neutrons, so many neutrons that calculations had suggested that it could *not* form. Yet Thomas Baumann and colleagues at the National Superconducting Cyclotron Laboratory at Michigan State University (MSU) in East Lansing produced 23 copies of the highly unstable nucleus, as they report this week in *Nature*.

"It's beautiful," says Olivier Sorlin, an experimenter at the French laboratory GANIL in Caen. "I'm quite surprised that they found it. We tried and did not succeed."

Aluminum-42 could cast a long shadow in the study of rare isotopes. Physicists plot the known nuclei on a gridlike chart with the number of protons running up the chart and the number of neutrons running across it. The nuclei lie in a broad swath that is bounded above by the so-called proton drip line, which shows which combinations of protons and neutrons are too rich in protons to form a nucleus, and below by the neutron drip line, which shows which combinations are too loaded with neutrons to stick together (see figure). According to two theoretical models, aluminum-42 lies on the wrong side of the neutron drip line and should not exist, even fleetingly.

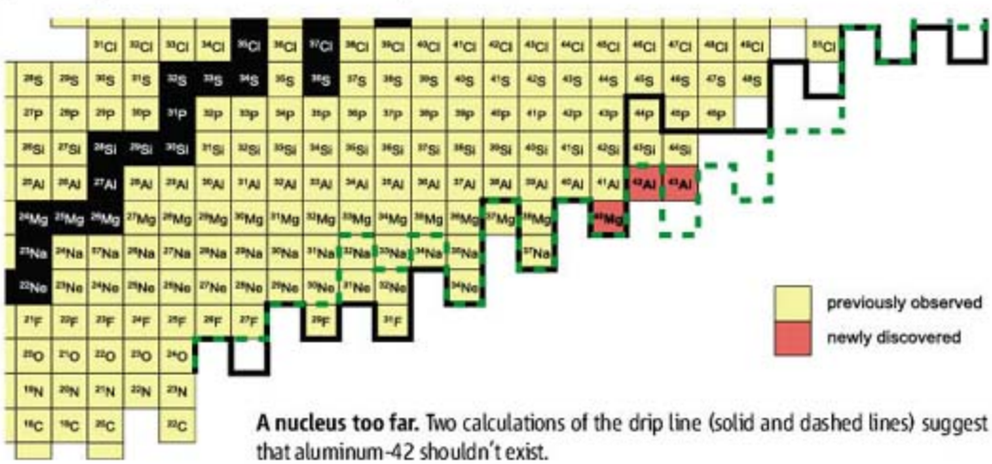
If aluminum-42 exists, then aluminum-43, -44, and -45 may also exist, says MSU's Michael Thoennessen. That's because aluminum-42 has one lone neutron in a "shell" that can hold as many as four. In fact, the team spotted one possible example of aluminum-43, as well as the nucleus magnesium-40. But the possibility that 32 neutrons could be packed into the aluminum nucleus means that the neutron drip line may lie too far away to be reached even with new facilities such as Japan's Radioactive Isotope Beam Factory at the RIKEN laboratory in Wako or Germany's Facility for Antiproton and Ion Research under construction at GSI in Darmstadt, Thoennessen says.

To make aluminum-42, the MSU team blasted calcium-48 nuclei, which have 20 protons and 28 neutrons, through a tungsten target. Very rarely, the violent collision stripped off seven of a calcium-48 nucleus's protons and gave it an extra neutron to make aluminum-42. To make aluminum-45, the incoming nucleus would have to snatch up four neutrons, an event so improbable that seeing it is "really at the edge of what's possible in any foreseeable future," Thoennessen says.

Not everyone is convinced that the drip line has retreated beyond reach. "It's an open question whether this [observation] pushes the drip line out generally or if there is a little bulge in that region" around aluminum, says Richard Casten of Yale University. Witold Nazarewicz, a theorist at the University of Tennessee, Knoxville, and Oak Ridge National Laboratory, says that the position of the drip line was not known precisely to begin with. "I think that most theorists would say that the models they looked at are simply not reliable for subtle details along the drip line," he says.

Even so, the existence of aluminum-42 undermines a key concept in nuclear physics, Sorlin says. Researchers know that nuclei with 28 neutrons are generally especially stable. So the fact that aluminum-42, with 29, holds together even for an instant suggests that the "magic number" 28 disappears at the drip line, Sorlin says. No matter where the drip line lies, aluminum-42 has given physicists plenty to think about.

–ADRIAN CHO



CREDIT: ADAPTED FROM T. BAUMANN *ET AL.*, *NATURE* (25 OCTOBER 2007)

A nucleus too far. Two calculations of the drip line (solid and dashed lines) suggest that aluminum-42 shouldn't exist.

Slow Down, You Move Too Fast

Physicists developing an engineering design for the proposed multibillion-dollar International Linear Collider (ILC) are getting ahead of themselves, Raymond Orbach, undersecretary for science at the U.S. Department of Energy (DOE), warned this week. Speaking at Fermi National Accelerator Laboratory in Batavia, Illinois, Orbach said physicists must follow the department's protocol that requires a large project to pass five critical decision milestones. The ILC has not passed the first, which allows researchers to proceed from basic R&D to design, Orbach said. Previously, DOE officials had been "completely open" to a less formal approach, says Caltech's Barry Barish, who leads the design team. What counts as "engineering design" remains to be determined, he says.

–ADRIAN CHO

Degrees of Magnitude in Russia

Russia has joined a Europe-wide effort to create a two-step progression in higher education that will shorten training for most students and save the government money. Last week's vote by the Russian parliament, in line with the 1999 Bologna process on higher education reform, creates a 4-year bachelor's degree and a 2-year master's degree that would replace the current 5-year degree that most students now receive. The change would go into effect in September 2009, although universities may implement it earlier.

Opponents complained that the law fails to spell out the new curriculum for the higher degree and restricts doctorate-seekers to those already holding a master's degree. But supporters said the changes address the country's labor needs by allowing students to graduate sooner and make the Russian degrees more compatible with those from the rest of Europe.

–VITALI LIPIK

Cell Research Fused

Chinese and Australian scientists are combining their stem cell expertise in a new partnership. The $1 million Australia-China Centre for Excellence in Stem Cells, announced this week, will forge a link between Peking University Stem Cell Research Center and Monash University Immunology and Stem Cell Laboratories. The new center's initial push will be using adult mesenchymal stem cells to treat cancer and diseases of the lung and liver, says Richard Boyd, director of the Monash lab. "Combining stem cell biology and immunology will push the field forward," adds Peking lab chief Li Lingsong.

–ELIZABETH FINKEL

NUTRITION

Dietary Guidelines Spark Flap Over Fish Consumption

Recommendations from a nonprofit group urging pregnant women to boost their fish consumption—contrary to U.S. guidelines—sparked widespread criticism earlier this month, in part because the review was funded by the fisheries industry. The advisory from the National Healthy Mothers, Healthy Babies (HMHB) Coalition has been dismissed by health advocates and government officials alike. Yet some researchers not involved in the furor say that industry sponsorship should not obscure the fact that fish consumption has plummeted because of federal guidelines—and that standards should be reconsidered.

In a statement issued on 4 October, HMHB and 14 researchers who reviewed the literature advised pregnant women to eat at least 12 ounces of fish each week to provide the developing fetus with brain-building omega-3 fatty acids. That contrasts with the position of the U.S. Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA), which in 2004 recommended that pregnant women consume no more than 12 ounces a week to limit their intake of mercury.

Caveat consumptor. A diet of fish during pregnancy can both help and harm a fetus's developing brain.

Government agencies reacted swiftly to HMHB's pronouncement. Three of HMHB's members—the National Institute of Child Health and Human Development, the Centers for Disease Control and Prevention, and the Health Resources and Services Administration—rejected the advice in a letter in *The Washington Post*. FDA and EPA announced that their guidelines wouldn't be changing.

Critics fault HMHB for accepting $60,000 from the National Fisheries Institute, an industry group, to disseminate the recommendations, along with honoraria of $1000 to $1500 per researcher. HMHB Executive Director Judy Meehan says the group gave no thought to how the industry funding would be perceived.

"People seem to have strong opinions" about fish consumption, but the science is "open to lots of interpretation," says Gary Myers, a pediatric neurologist at the ▶

PUBLIC POLICY

Watson Condemned for Comments on Intelligence

James Watson visited the United Kingdom this month to promote his new book, *Avoid Boring People: Lessons from a Life in Science*. But the tour came to a premature and ignominious end last week after the 79-year-old Nobelist told a British newspaper that, in effect, blacks are less intelligent than whites. As *Science* went to press, Watson was back in the United States hoping to save his job as chancellor of Cold Spring Harbor Laboratory (CSHL) in Long Island, New York.

Watson has been the lab's most public face for nearly 40 years, serving as director and then president before becoming chancellor in 2004. His current responsibilities include fundraising for the 117-year-old nonprofit and helping transform it into a university. But the lab's board of trustees, of which he is a member, moved swiftly to distance the institution from him after he was quoted in the 14 October *Sunday Times* as saying that he was "inherently gloomy about the prospect of Africa" because "all our social policies are based on the fact that their intelligence is the same as ours—whereas all the testing says not really."

Crossing the line? James Watson was suspended as chancellor of Cold Spring Harbor Laboratory following his remarks last week.

Watson's comments in "no way reflect the mission, goals, or principles of Cold Spring Harbor Laboratory's Board, administration, or faculty," explained CSHL President Bruce Stillman on 17 October. "Cold Spring Harbor Laboratory does not engage in any research that could even form the basis of the statements attributed to Dr. Watson." In a second statement the next day, the board said it was suspending Watson "pending further deliberation." As *Science* went to press, Jim Bono, a spokesperson for CSHL, said a decision was expected in the next few days.

Watson has a history of making sweeping remarks, including his suggestion in 2000 that libido is linked to exposure to sunlight. But this time he seems to have gone too far. "You get to the end of the rope at some point," says one trustee who spoke to *Science* on the condition of anonymity. "The feeling was that something very inappropriate had occurred and some action needed to be taken."

Watson has apologized for the remarks, which also prompted London's Science Museum to cancel a scheduled talk. "I cannot understand how I could have said what I am quoted as having said," he told The Associated Press. "To all those who have drawn the inference from my words that Africa, as a continent, is somehow genetically inferior, I can only apologize unreservedly." But in a 19 October commentary published in *The Independent*, Watson seemed also to put up a defense. "The overwhelming desire of society today is to assume that equal powers of reason are a universal heritage of humanity," he wrote. "It may well be. But simply wanting this to be the case is not enough. This is not science."

Neither were his own comments, says Harvard University psychologist Howard Gardner. "He has taken an extremely complex set of issues—what is intelligence, what is race, how valid are IQ tests—and reduced them to a provocative sound bite," says Gardner. As someone "of almost unique prestige in the scientific community," Gardner notes, Watson "has a special responsibility to watch his tongue." **–YUDHIJIT BHATTACHARJEE**

CREDITS (TOP TO BOTTOM): DPA/LANDOV; EDMOND TERAKOPIAN/PA PHOTOS/LANDOV

University of Rochester in New York who has helped lead a major study of fish consumption in pregnancy, in the Seychelles northeast of Madagascar. He and others say it's difficult to identify the tipping point at which the risks of mercury in fish outweigh the benefits of omega-3 fatty acids.

The topic also pits scientific disciplines against each other. "Environmental health people see the effects of mercury on the brain and get scared; nutrition people says there's this great nutrient and people aren't getting enough," says Emily Oken, a nutrition researcher at Harvard Medical School in Boston who focuses on women's health. In her own study of 135 babies and their mothers, Oken found that higher fish consumption boosts cognition at 6 months of age, whereas mercury levels, measured in a mother's hair, decrease it. But on balance, she wrote in a 2005 paper in *Environmental Health Perspectives*, more fish in the diet was still associated with better cognition.

In general, scientists note that both the benefits and drawbacks of fish are small for individuals, although they can be significant across a population. Exposure is usually measured as mercury in maternal hair. Some studies show that an increase in this index is linked to very subtle cognitive changes, including reduced word recall and a 1-point loss in IQ. HMHB's guidance gave little weight to the risks of mercury and did not recommend that pregnant women avoid high-mercury fish.

Even some who worry that pregnant women consume too little fish say that HMHB's guidelines focus too much on the benefits of fish, just as the federal recommendations are faulted for overemphasizing the risks. In response, Patricia Nolan, a public health physician at Brown University who helped craft the HMHB recommendations, said in an e-mail that "we emphasized the positive because women are decreasing or eliminating already low fish consumption."

But what's really needed, says David Bellinger, a neuropsychologist at Harvard Medical School, is a more nuanced review that would give pregnant women a fuller picture of how specific types and quantities of fish in the diet could affect their baby-to-be.

–JENNIFER COUZIN

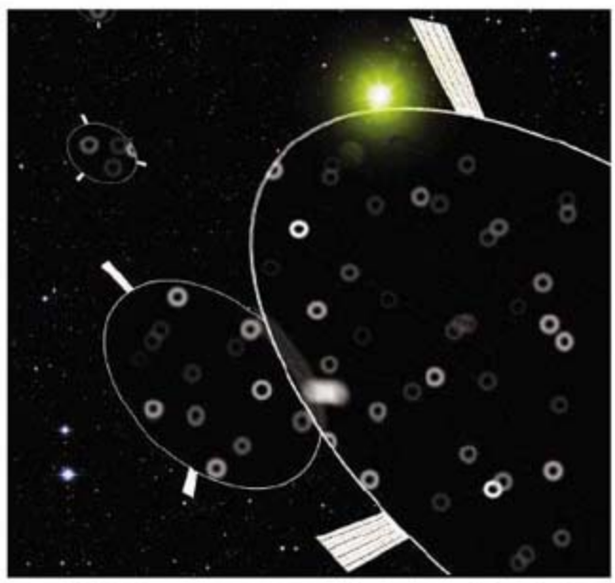
GLOBAL CHANGE

Tinkering With the Climate to Get Hearing at Harvard Meeting

Should scientists and engineers seriously consider large-scale alterations of the climate to stave off the worst effects of global warming? Several dozen top U.S. climate scientists will explore that controversial question next month in a 2-day invitation-only workshop at Harvard University designed to explore whether direct interventions might be needed to supplement efforts to reduce greenhouse gas emissions.

Curbing greenhouse warming manually, so to speak, could offer a more immediate and possibly simpler solution to climate change than the massive overhaul of energy systems that would be needed to cut global greenhouse gas emissions. Ideas include removing CO_2 from the atmosphere by forcing air through absorbers or stimulating plankton growth, and shading the planet with aerosols. But many prominent climate scientists have been leery of even discussing such possibilities for fear that they could provide policymakers with an excuse not to cut carbon emissions, or that the technology comes with serious side effects. As a result, says Harvard geochemist Daniel Schrag, who is organizing the meeting, discussions have occurred mostly among advocates. "I wanted to get the mainstream climate community … to look closely at this thing," he says.

The 8 to 9 November meeting will include climate heavyweights such as James Hansen of NASA, Kerry Emanuel of the Massachusetts Institute of Technology in Cambridge, and Mark Cane of Columbia University. Its focus will be on ways to lower the atmosphere's temperature, including releasing massive amounts of sulfates into the atmosphere to mimic the natural cooling effects of volcanic eruptions. Such an approach was publicized last year by Nobelist Paul Crutzen, an atmospheric chemist at the Max Planck Institute for Chemistry in Mainz, Germany (*Science*, 20 October 2006, p. 401).



Solar shield. The University of Arizona's Roger Angel has calculated that trillions of orbiting disks could refract sunlight and reverse catastrophic global warming.

Scientists pondering geoengineering ideas argue that such cooling schemes could be hard to control and wouldn't address the acidification of the oceans caused by CO_2. Others worry that any discussion of the topic will undermine political momentum to cut greenhouse gas emissions. These include atmospheric scientist Elisabeth Moyer, who before leaving Harvard for the University of Chicago told Schrag that the conference should be held off campus or without publicity. "I had concerns about lending the conference the prestige of the Harvard name. … The conference can be viewed as an endorsement [of geoengineering]," she says. Even so, Moyer thinks that "it is critical to discuss the idea."

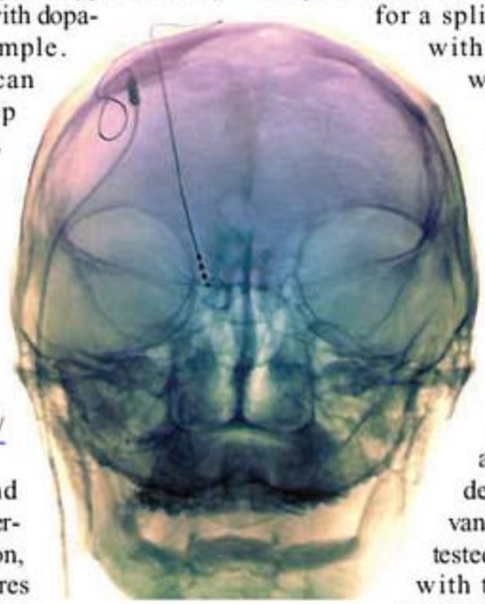
Hansen says better forest practices, advanced agriculture techniques, and geologic carbon sequestration could supplement the real emission cuts required to stave off dangerous climate change and avoid the need for geoengineering efforts. He hopes to spread that message at the meeting. "The potential for stabilizing climate is more than realized," he says. But he agrees with Schrag that geoengineering should still be explored, as future policymakers might seek to do it whether or not scientists understand it. "I don't think scientists should shy away" from the topic, he says.

The fact that the meeting is taking place at all marks a new phase of urgency among climate scientists, says modeler Ken Caldeira of the Carnegie Institution of Washington in Stanford, California. In a 1998 paper, Caldeira called the aerosol approach "a promising strategy," although he argued that emissions cuts remain "the most prudent" course of action. "A decade later, a bunch of people are coming to the same point," says Caldeira. **–ELI KINTISCH**

NEUROSCIENCE

Two Therapies Release Different Brakes on Impulsive Behavior

To unlock rigid limbs and restore their mobility, people with Parkinson's disease often require strong therapy, such as drugs that boost levels of the neurotransmitter dopamine—and if that fails, stimulating electrodes implanted deep in the brain. Yet these treatments can trigger impulsivity: Pathological gambling and hypersexuality have been associated with dopamine drugs, for example. Impulsive behavior can also accompany deep brain stimulation (DBS), but the electrical treatment promotes it in different ways than the drugs do, according to a study published online this week by *Science* (www.sciencemag.org/cgi/content/abstract/1146157).



Wired. Deep brain electrodes may stimulate impulsivity as well as mobility in Parkinson's patients.

Michael Frank and colleagues at the University of Arizona, Tucson, report that DBS interferes with patients' normal tendency to hesitate when faced with a difficult decision, whereas dopamine drugs interfere with the ability to learn from bad experiences. Although the study doesn't immediately point to ways to counteract such impulsive tendencies, other researchers say that the work does shed light on the neural mechanisms that control our thoughts and actions. "It's an advance towards understanding the architecture of cognitive control in the human brain," says Adam Aron, a cognitive neuroscientist at the University of California, San Diego.

Frank and his team used a computer game to investigate decision-making in 15 people with Parkinson's disease taking dopamine drugs and 17 patients receiving DBS targeted to the subthalamic nucleus, part of the network of brain regions disrupted by the disease. In the initial learning phase, the participants saw pairs of unfamiliar squiggles (actually Japanese hiragana characters) and were told, without further instruction, to pick the one that was "correct." Unbeknownst to the subjects, each character had a fixed success rate: In one pair, for instance, one character caused the word "Correct!" to flash on the screen 80% of the time, whereas the other was correct the remaining 20% of the time. With practice, the people generally picked the character with the highest success rate.

Next, the researchers presented new pairings of the same characters. Healthy subjects and medicated patients hesitated for a split second when faced with a pair of characters with similar success rates. DBS patients, on the other hand, made faster choices when the alternatives were similarly attractive. This tendency to rush close calls vanished when researchers tested the same DBS patients with the stimulating electrodes turned off. The findings, says Frank, bolster his group's suggestion that when a difficult decision presents itself, the normal role of the subthalamic nucleus is to send a "hold your horses" signal to other parts of the brain to allow more time to weigh the options. DBS interferes with this signal, leading to hasty choices, Frank hypothesizes.

Dopamine-boosting drugs had no effect on the speed of decisions, but they did reduce patients' tendency to avoid bad choices that had burned them in the past (such as picking the character with a 20% success rate). That fits with previous work, and it may help explain why some medicated patients with Parkinson's disease keep gambling despite repeated losses, says cognitive neuroscientist Roshan Cools of Radboud University Nijmegen in the Netherlands.

"What's really novel is the argument here that there are multiple pathways by which these impulsive behaviors can occur," says Cameron Carter, a cognitive neuroscientist at the University of California, Davis.

–GREG MILLER

The Million-Dollar Genome

Beijing Genomics Institute's (BGI's) Shenzhen branch made a splash this month with the announcement that it had sequenced the first complete genome of a Chinese individual, the third personal genome sequenced this year, after those of J. Craig Venter and James Watson. Now the new kid on the genome block is offering its service to any Chinese who can plop down $1.3 million.

BGI Shenzhen, also known as Shenzhen Huada, was incorporated last April as a nonprofit research organization funded primarily by local governments. The institute plans to sequence 99 more Chinese genomes as part of a 100-person project to map DNA polymorphisms in the Chinese population. To help finance the endeavor, Shenzhen Huada is offering wealthy Chinese the opportunity to have their own genome completely sequenced and analyzed. Forty percent of the income will go to a foundation to support Shenzhen Huada's health-related genomic research, including a plan to sequence 10,000 genomes of the dominant Han and ethnic minority Chinese as well as other East Asians, says BGI Director Yang Huanming. Another project sequencing the panda genome is already under way. –HAO XIN

Updates

- The ITER Organization—which aims to show that nuclear fusion is a viable power source—came into being this week, 2 decades after the idea was proposed. The European Union and six member nations have ratified the necessary agreement and will now begin building a €5 billion reactor in Cadarache, France.

- Last week, six universities joined the ranks of the German elite. Government officials announced the winners of a second round of funding designed to boost a few top universities to world-class status (*Science*, 20 October 2006, p. 400). Winners this time were the RWTH Aachen University, Freie Universität Berlin, the University of Freiburg, the University of Göttingen, the University of Heidelberg, and the University of Konstanz. They join last year's three winners in receiving an extra €3 million a year in federal funding for the next 5 years.

- Hundreds of French researchers gathered last week at the headquarters of the National Centre for Scientific Research to protest the government's alleged plans to turn the $4.3 billion institute into a funding agency. The government will announce its plans for CNRS later this year.

ARCHAEOLOGY

University Suppresses Report on Provenance of Iraqi Antiquities

University College London (UCL), one of Britain's premier universities, has become embroiled in a dispute over its handling of a large collection of religious artifacts that may have been part of the illicit trade in archaeological relics from Iraq in recent years. Last year, a committee of experts UCL established to investigate the matter concluded that "on the balance of probabilities," the artifacts were illegally removed from Iraq, and in the past months Iraqi officials have taken steps to recover the relics. Their actions come after UCL agreed this summer to return the collection to its owner, a wealthy retired Norwegian businessman who had sued UCL for their recovery. As part of a settlement of that suit, UCL agreed not to publish the committee's report.

"It is shameful that a university should set up an independent inquiry and then connive with the collector whose antiquities are under scrutiny to suppress the report through the vehicle of an out-of-court settlement," says Colin Renfrew, an archaeologist at the University of Cambridge, U.K., and a longtime critic of trade in antiquities of questionable provenance. Renfrew was one of three experts appointed by UCL in early 2005 to look into allegations about the provenance of the Aramaic incantation bowls and to propose new antiquities guidelines. Neil Brodie, an archaeologist at Stanford University in Palo Alto, California, and former research director of Cambridge's Illicit Antiquities Research Centre—created by Renfrew in 1996—calls suppression of the report "an attack on academic freedom, because the illegal trade in antiquities is a legitimate research subject."

Salah al-Shaikhly, Iraq's ambassador to the United Kingdom, told *Science* last week that Iraqi authorities have asked British authorities to block the export of the bowls and that the Iraqi government hopes to go to court to recover the bowls "in a matter of weeks." The removal of the artifacts, al-Shaikhly says, is "a great loss to the Iraqi national heritage."

The affair has also caused considerable discomfort within the university's Institute of Archaeology, which has played a leading role in developing strict antiquities rules. "I deeply regret the fact that the panel's report will not be published," says UCL archaeologist Kathryn Tubb, who co-wrote the institute's guidelines. "The results of the deliberations were to have informed future policy for the whole of UCL."

UCL officials have refused to comment on the matter, and Martin Schøyen, the owner of the bowls, declined to be interviewed for this story. But a series of press statements on the Schøyen Collection's Web site (www.schoyencollection.com/news.htm) explains that "any assertion that the bowls in the Schøyen Collection might be looted is incorrect." The Web site notes that the artifacts came from a Jordanian collection "built over many years."

The UCL committee of inquiry's report—a copy of which *Science* has reviewed—concludes that the bowls most likely left Iraq illegally sometime after August 1990, when Iraq invaded Kuwait. Schøyen subsequently bought them from dealers based in Jordan and London. The 94-page report says that the committee found "no direct evidence that positively contradicts or impugns Mr. Schøyen's honesty" in his account of how he obtained the bowls and credits him with "openness" in the way he purchased them. But it sharply criticizes UCL for agreeing to store the bowls without looking into their origins or "the manner in which Mr. Schøyen came to possess them."

"It is shameful that a university should set up an independent inquiry and **then ... suppress the report through ... an out-of-court settlement."**

—Colin Renfrew, University of Cambridge

"A potentially damaging position"

During the 5th to 8th centuries C.E., many people living in Mesopotamia (present-day Iraq) buried pottery bowls under the thresholds of their houses to ward off evil demons. The bowls were inscribed with biblical passages and other incantations in Aramaic, an ancient Semitic language. Today, about 2000 of these Aramaic incantation bowls are known to exist in public and private collections around the world. Schøyen owns one of the two largest collections, numbering 656, and beginning in 1995, loaned 654 of them to UCL's Department of Hebrew and Jewish Studies to be cataloged and studied. The research was led by linguist Shaul Shaked of the Hebrew University of Jerusalem, in collaboration with UCL's Mark Geller, an expert in ancient languages.

In September 2003, a documentary aired on Norwegian public television that questioned the provenance of a number of antiquities in Schøyen's collection—which is based in Oslo and London—including the incantation bowls. According to the committee's report, questions from the program's producers led UCL Vice-Provost Michael Worton to write Geller on 2 December 2003, directing him to make arrangements to

CREDITS (TOP TO BOTTOM): COURTESY OF ERICA HUNTER; QFT PHOTOGRAPHY LTD., COURTESY OF C. RENFREW

Away all demons! Ancient Mesopotamians used bowls inscribed in Aramaic to repel evil spirits.

return the artifacts to Schøyen—an order that the report says was never carried out. (Both Worton and Geller declined to comment on this and other matters related to the bowls.) UCL also consulted its attorney, who, according to the committee report, told UCL on 10 September 2004 that it was in "an anomalous and potentially damaging position" because it might be violating international and British antiquities laws by keeping the bowls—or returning them to Schøyen—if the bowls had been removed illegally from Iraq.

In early 2005, UCL set up the committee of inquiry that, Worton explained in a 16 May 2005 press release, would allow UCL "to be absolutely clear about the provenance of these bowls, and to satisfy ourselves that they were not removed illegally from their country of origin." He said the committee's report would also "provide a model for best practice in dealing with the complex cultural issues that can arise from such situations."

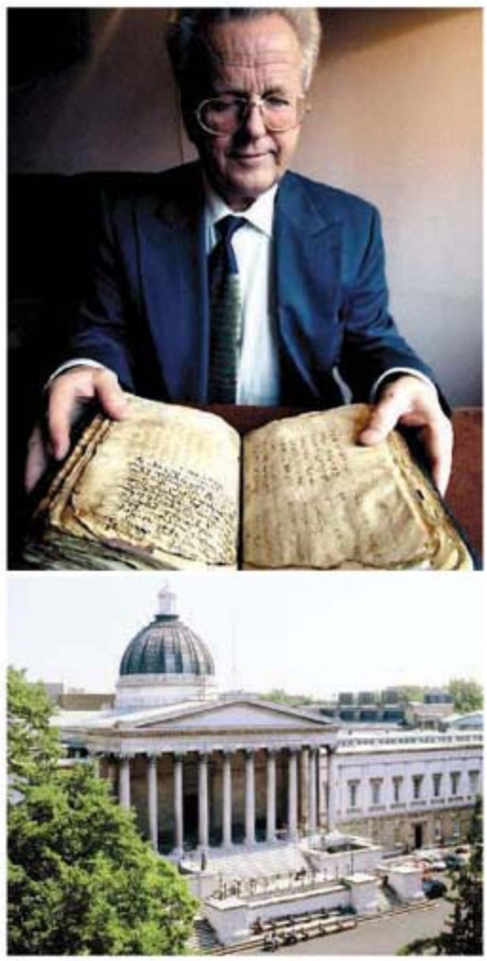
The committee—comprised of David Freeman of the London law firm Kendall Freeman; Sally MacDonald, now director of UCL Museums and Collections; and Renfrew—took testimony from three dozen witnesses, including Schøyen and two London-based antiquities dealers who, the committee determined, sold him many of the incantation bowls. Schøyen and the dealers told the committee that nearly all of the bowls had come from the family collection of Ghassan Rihani, a Jordanian antiquities dealer who reportedly died in 2001. But the committee found "unconvincing" two Jordanian documents that Schøyen offered in support of his claim that the incantation bowls had been legally transferred from Jordan to London.

In an interview with *Science*, one of the two London dealers, Chris Martin, says that Rihani had some incantation bowls in his collection at least "3 or 4 years" before the 1991 Gulf War. The committee calculated that Martin sold Schøyen 444 of the incantation bowls, of which at least 300 came from Rihani. After a time, Martin says, Schøyen began to buy directly from Rihani and, according to the report, acquired another 174 bowls this way.

The committee's report cites the testimony of four experts in ancient Mesopotamia that nearly all known incantation bowls come from Iraq, which since 1936 has forbidden the export of antiquities except for exhibitions and research. "The bowls were present in Iraq when the 1936 Law came into force … [and therefore] were the property of the State of Iraq" at the time that Schøyen purchased them, the report concludes, even if Schøyen may not have realized this. Nevertheless, the committee found that, under U.K. law, Schøyen could still claim title to the bowls if he had already possessed them for 6 years and could demonstrate that he had bought them in good faith.

Claiming the bowls

The committee's report, dated 27 July 2006, contains a number of recommendations, including that it "be published in full." Indeed, Renfrew told *Science*, the panel prepared the report "in the expectation that it would be published." Nevertheless, the panel proposed delaying publication for 6 months while copies were sent to Schøyen, the antiquities departments of Iraq and Jordan, London's Metropolitan Police, and two other British government agencies. Although UCL officials have declined to comment on any aspect of the affair, Renfrew says UCL attorneys told the committee early in 2007 that the university would "omit the legal arguments and conclusions and recommendations" in summaries being sent to Iraq, Jordan, and the police.



The collector. Martin Schøyen (*top*) sued University College London (*below*) to get back his artifacts.

The report has not been published, however. On 9 March 2007, the Schøyen Collection announced that it was suing UCL to recover the incantation bowls. A press release explained that it "has become frustrated with the waste of time and money caused by a lengthy and inconclusive inquiry into its provenance" and added that it had "los[t] confidence in UCL's conduct of its inquiries."

Meanwhile, on 26 June, Schøyen and UCL issued a joint press statement signaling an end to the litigation. "Following a searching investigation by an eminent panel of experts, and further inquiries of its own," the statement declared, "UCL is pleased to announce that no claims adverse to the Schøyen Collection's right and title have been made or intimated" and that "UCL has no basis for concluding that title is vested other than in the Schøyen Collection." The bowls have been returned, the statement said, "and UCL has agreed to pay a sum in respect of its possession of them."

Jenina Bas, media spokesperson for the Schøyen Collection, declined to say where the bowls are now located, citing "security reasons." However, Shaked told *Science* that they are still in the United Kingdom. Al-Shaikhly says that Iraq did not immediately make a claim on the bowls because "lawyers in England are very expensive." He adds that culture ministry officials in Baghdad discussed the matter for several months before agreeing to proceed.

In the meantime, Shaked says that he plans to continue his research. "It is my responsibility as a scholar to work on any ancient artifact that has information to tell us," he told *Science*, staking out one side of a bitter debate among archaeologists about whether researchers should work with unprovenanced antiquities (*Science*, 28 April 2006, p. 513). The other side believes that researchers and collectors are morally obligated to carry out what archaeologists call "due diligence" into the provenance of the antiquities they work with. "Due diligence is at the heart of the discussion about the antiquities market," says archaeologist David Gill of Swansea University in Wales. "If respected international institutions are unable or unwilling to release the findings of this process, archaeologists begin to smell a rat."

Renfrew agrees with Gill's assessment of the situation. He calls suppression of the report a "huge mistake" and believes it was motivated by the university's desire to avoid a costly legal battle. "If so," Renfrew says, "they have sold their souls for a mess of pottage."

–MICHAEL BALTER

CREDITS (TOP TO BOTTOM): SCANPIX/SIPA PRESS; UNIVERSITY COLLEGE LONDON

Battling Over Bed Nets

A collision of big thinking and logistical realities has sparked an intense debate over how best to deliver bed nets to combat malaria in Africa

JEFFREY SACHS IS AN IMPATIENT MAN. In a widely promoted editorial in *The Lancet* on 21 June, the economist, public health advocate, and head of Columbia University's Earth Institute lit a fire under the organizations and individuals involved in battling malaria. He called on international donors, in essence, to blanket sub-Saharan Africa in insecticide-treated bed nets (ITNs)—for free, and right now.

The delay in delivering bed nets "is one of the shocking crimes of our time," says Sachs. He blasts donors for trying to save money instead of lives by targeting nets only to the most vulnerable groups, pregnant women and young children—and often charging the recipients a modest fee. That strategy penalizes the poor, who can't afford to pay, and fails to take full advantage of the "herd effect" nets can provide by reducing the numbers of mosquitoes that transmit the disease, Sachs argues. By contrast, providing one bed net for every sleeping space—which he estimates would cost about 60 cents a year per person—could slash malaria transmission in Africa by 90%, he says. In the absence of a vaccine, he maintains, free universal bed-net distribution, accompanied by rapid access to state-of-the-art antimalaria drugs, is *the* best solution to Africa's malaria crisis, which kills an estimated 1 million people a year.

It sounds simple, and it's hard to argue with the goal, especially against someone of Sachs's stature. But some malaria experts disagree vehemently on whether such a grand plan is feasible, much less desirable. "There is no universal one-size-fits-all solution to malaria," says malaria researcher Christian Lengeler of the Swiss Tropical Institute in Basel, who says he has developed a different perspective from 15 years of working on the ground in Africa.

Without question, bed nets are the best intervention available to prevent malaria. And everyone agrees that coverage, although rising, remains far too low. But they differ on whether giving a net to almost everyone, adults and children alike, is the best use of scarce resources. Critics complain that a big new program would disrupt existing strategies for malaria control that have worked reasonably well, if not perfectly. And they question whether donors would continue to foot the bill once malaria cases plummet and other diseases become relatively bigger killers of Africa's children.

"These are real substantive issues," says Mark Grabowsky, the malaria program manager at the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which was created in 2000 to help the world's poorest countries fight those diseases. "There are true believers on both sides," agrees Richard Steketee, the science director of the nonprofit Malaria Control and Evaluation Partnership in Africa, headquartered in Seattle, Washington, which is helping Zambia scale up its ambitious malaria-control program.

Sachs did win a key endorsement from Arata Kochi, head of the Global Malaria Programme at the World Health Organization (WHO). In late August, Kochi announced that WHO would now recommend universal access to bed nets, free or at sharply reduced costs. Data just in from Kenya, showing a 44% drop in mortality following a huge upswing in bed-net coverage, "ended the debate" on how best to distribute them, Kochi said.

That may have been wishful thinking on Kochi's part. When Sachs started promoting his idea—which he estimates would cost $3 billion a year, including drugs—he touched a raw nerve in the malaria community, exposing existing fissures and reopening old wounds, and the debate has taken a nasty personal turn. As special adviser to directors general of the United Nations, past and present, and chief architect of the Millennium Development Goals, Sachs commands the global bully pulpit like few others. And he has used it to denounce those who resist his plan as obstructionists and even immoral.

They, in turn, accuse Sachs of heavy-handed interference in country policies and of almost monomaniacally pushing his view to the exclusion of all others. "There is one way to do things, and that is Sachs's way," says Nick Brown, who coordinates bed-net efforts for the National Malaria Control Programme in Tanzania, where these issues have recently come to a head.

CREDIT: WENDY STONE/CORBIS

Simple solution. Decidedly low-tech, insecticide-treated bed nets are one of the most effective tools for preventing malaria.

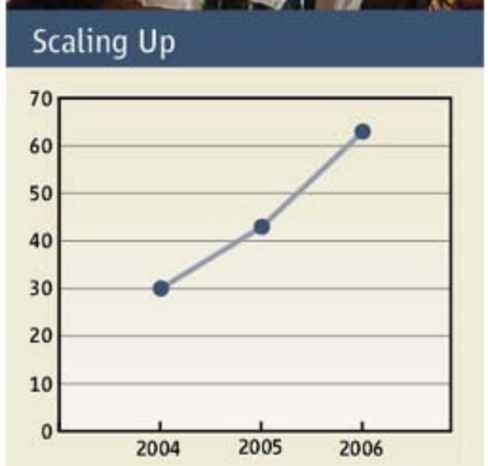
Net work

Nobody disputes that ITNs work. A series of big clinical trials in Africa in the 1990s consistently showed a 20% drop in childhood mortality from regular ITN use. Even untreated nets protect against mosquitoes, at least until they rip. And the treated versions work even when they are torn, because they not only block contact but also repel or kill the mosquitoes that transmit the malaria parasite. Until recently, however, they have had to be retreated at least yearly, a significant hurdle. New long-lasting nets that are effective for 5 years are helping solve that problem.

Lack of money for malaria control has been the big barrier to widespread net distribution. Over the years, donors and countries alike have scrambled to stretch dollars to get nets to where they would do the most good. That limitation gave rise to the consensus strategy—adopted in the late 1990s by WHO, the Roll Back Malaria Partnership, and donors such as the World Bank, the U.S. Agency for International Development, and the U.K. Department for International Development—of targeting those most likely to die from malaria: pregnant women and children under age 5. And because dollars were short, donors, health workers, and researchers also threw their support behind a strategy known as social marketing, which involves priming, or in some cases creating, a commercial net industry that, in principle, could help make nets available at prices most people could afford.

This was the approach adopted in Tanzania, long held up as a model for Africa. The program there focused on "creating a net culture": convincing people of the benefits of sleeping under nets and shoring up a retail industry to provide them. Because much of the country is too poor to pay full price, a voucher system was created to provide subsidized nets to the most vulnerable groups. Distributed at antenatal clinics, the printed vouchers entitled a pregnant woman to get an ITN for about $1 or $1.50, instead of $3 or $4. "It was the paradigm," says Lengeler, who helped develop the Tanzania program.

At a Roll Back Malaria summit in Abuja, Nigeria, in 2000, the leaders of malaria-affected countries set a target of getting bed nets to at least 60% of the vulnerable groups by 2005, a target that has since been boosted to 80% by 2010. But progress has been painfully slow. By 2002, less than 5% of African children, on average, were routinely sleeping under a bed net. And a disturbing inequity has persisted: Coverage across Africa has been far lower among the rural poor, who are at greatest risk of malaria, than among urban and wealthier people.



Number of insecticide-treated bed nets produced worldwide, 2004–2006 (millions).

Sea change

All that began to change about 2003, with the congruence of a big jump in funding for malaria, new evidence that nets work even in the most challenging settings, and new models for net distribution.

Thanks in no small part to the advocacy of Sachs and others and the entry of big donors such as the Global Fund, the Bill and Melinda Gates Foundation, the World Bank, and the U.S. President's Malaria Initiative, global funding has increased more than 10-fold over the past decade. Between 2003 and 2006, the Global Fund alone pumped $1.7 billion into malaria, and the number of bed nets it distributed in Africa surged from 1.35 million to 18 million. Available funds continue to climb, says Grabowsky: "The rate-limiting step is no longer money but the ability of countries to absorb it."

Also in 2003, the last of the five big clinical trials of ITNs in Africa provided the firmest evidence yet of the so-called community effect, akin to the herd effect provided by vaccines. People in nearby control villages who weren't sleeping under nets experienced a substantial drop in malaria mortality as well. That's because ITNs, which in the trial were targeted to the entire household and not just vulnerable groups, were reducing the vector population and thus the chances a person would encounter an infected mosquito.

The new results from Kenya changed perceptions. They meant that bed nets, like vaccines, should be seen "as a public good, worthy of public support," wrote William A. Hawley of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and other leading malaria researchers in an accompanying article in *The American Journal of Tropical Medicine and Hygiene*. To make a real dent in malaria, everyone should have a bed net, Hawley and colleagues proposed. And increasingly, experts such as Sachs and colleagues Christopher Curtis of the London School of Hygiene and Tropical Medicine and Awash Teklehaimanot of the Earth Institute were saying bed nets should be free.

Exactly how many nets are needed for maximum impact is hard to quantify. A 2007

Voucher scheme. Women in Tanzania receive vouchers at antenatal clinics, which they can redeem at local shops to purchase subsidized bed nets.

CREDITS (TOP TO BOTTOM): MARKO KOKIC/REUTERS/LANDOV; SOURCE: UNICEF; CHRISTIAN LENGELER

study by Gerry Killeen of the Ifakara Health Research and Development Centre in Tanzania and others, including Lengeler, suggests that 60% coverage of all adults and children is enough. Sachs thinks it is closer to 80% and argues that the cost is so low, it is absurd to settle for less than full coverage. Whatever the number, "there is likely some incremental value to every bed net in the community," says Grabowsky.

People widely credit Grabowsky for coming up with the model that would transform net delivery. Then in charge of measles vaccination for Africa for the American Red Cross, Grabowsky decided to piggyback ITN delivery onto the measles infrastructure. Pilot projects in Ghana and Zambia in 2002 and 2003 began giving out free bed nets to every family with a child younger than 5 years old during measles vaccination campaigns.

The first nationwide campaign was launched in Togo in 2004: Over the course of 7 days, about 900,000 nets were distributed free of charge, and the number of households owning a bed net skyrocketed from 5% to 91%, says Grabowsky, who adds that education is essential to ensure that ownership translates into use.

The delay in delivering bed nets **"is one of the shocking crimes of our time."**

—Jeffrey Sachs, Earth Institute, Columbia University

Sachs raves about the results. These joint campaigns "have the capacity to reach the very isolated rural areas in the poorest countries," Sachs told *Science*. "It is astounding how much coverage it is possible to get in these campaigns. In Togo, Sierra Leone, Niger, a 1- or 2-week campaign gets 70% to 80% coverage."

Other countries and donors, such as the Global Fund and the U.S. President's Malaria Initiative, took the cue. Since then, there have been a dozen more mass campaigns, in Ethiopia, Kenya, Niger, São Tomé and Príncipe, Angola, and Rwanda, to name a few, usually integrated with measles immunization or other childhood interventions. One of the biggest is now under way in Zambia, which is on target to provide bed nets to 80% of the population by 2008 (see sidebar).

Free for all

That's the model Sachs wants to capitalize on. But rather than giving nets to children only, he wants countries and donors to give out enough nets for every sleeping space, roughly three per household. This would protect children and adults alike and remove the reservoir of infection, taking full advantage of the net's community effect. He thinks it should be done within 4 years, if not sooner.

Who could be opposed? asks Lengeler: "In theory, we would all love to do it." But in reality, he and others say, it might not be the best strategy to try to reach almost every person in Africa, especially single men, who have no regular point of contact with the health system. Early in the Zambian effort, for instance, the military was engaged after nets sat around unused for months, says Steketee, who concedes that campaigns are taxing, time-consuming, and hard to organize, but worth it. Skeptics say discussions of Sachs's plan tend to gloss over those difficulties. And even Sachs's staunchest supporters agree, confidentially, that although he is a brilliant advocate for malaria, his genius does not lie in such operational details.

Lengeler also questions whether Sachs's scheme is worth the cost, because covering even half the population still provides considerable community protection. He suggests donors could get a bigger bang for the

A PROOF OF PRINCIPLE

What if money were no object and you could employ all the weapons that exist today to fight malaria in one country? How much could you reduce mortality? That experiment, known as the Malaria Control and Evaluation Partnership in Africa (MACEPA), is going great guns in Zambia.

A collaboration of the Zambian government, the various Roll Back Malaria partners, and the nonprofit PATH (Program for Appropriate Technology in Health) in Seattle, Washington, the Zambia project is employing long-lasting insecticide-treated bed nets, indoor spraying with insecticides, and rapid access to the most effective antimalarial drugs, artemisinin-based combination therapies. Started in 2005 and funded by the Bill and Melinda Gates Foundation, the World Bank, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria, the goal of the project is to slash malaria mortality 75% by 2008, an achievement that has been estimated to cost between $30 million and $50 million a year. It is well on its way to achieving that goal, says the scientific director of MACEPA, Richard Steketee of PATH.

With MACEPA's support, the Zambian government aims to deliver bed nets to 80% of the population, adults and children alike, by the end of 2008. The first year was not a rousing success. The partners finally called on the military to help distribute the 526,500 nets that were sitting unused in Lusaka—the running joke is that they probably spent more on gas than on nets. For the second shipment of 200,000 nets, they settled on a decentralized plan. Nets are now delivered directly to districts where health-management teams work with local leaders to arrange big community events where people come to pick up their nets. Health teams are trained to explain why and how nets should be used, a key component in any net-distribution strategy, says Steketee. It is working, he says. Last year, 1 million nets were distributed, and this year, the target is 3.4 million. "By the end of the year, we will be close to covering the entire nation with three nets per household."

Bold experiment. Zambia hopes to slash malaria mortality by 75% by 2008.

Mass campaigns are supplemented by net distribution during vaccination campaigns and at antenatal clinics, where women pay about 50 cents for a net, although next year, nets may be provided for free, says Steketee.

Of course there are problems and nets that go undistributed, he says. "But we have seen a huge drop in malaria. Houses with nets have way less malaria and less severe anemia in young kids. It is entirely consistent with the data from controlled trials." And although final data on mortality reduction won't be available for a year or two, evidence so far "consistently shows a good number of lives are being saved." **–L.R.**

CREDITS (TOP TO BOTTOM): KATIE ORLINSKY/BLOOMBERG NEWS/LANDOV; PATH

buck by doubling the salary of health-care workers in Africa and ensuring regular drug supply instead.

The program in Tanzania, where 95% of the population lives in highly malarial regions and the disease claims 100,000 lives a year, has become a battleground in this debate. In many ways, the national malaria-control program, which received one of the first grants from the Global Fund in 2003, has been a success, says Brown, who coordinates the program's ITN efforts. The country now boasts four domestic net manufacturers and some 5700 retailers, mostly small stores that also sell soap, sugar, and batteries. But bed-net coverage hasn't climbed as fast as anyone would like, and it has remained stubbornly low among the rural poor. By 2006, "we covered 35% of the children and 25% of adults," says Lengeler. "That is clearly too low. … We accept the criticism."

The various partners working in Tanzania set out to fix those problems last spring, holding a series of meetings to chart a way forward. The debates were intense, with some arguing to jettison the voucher scheme, and Lengeler, Brown, and many of the donors saying don't throw the baby out with the bath water.

One of their chief concerns was that Sachs's plan would destroy the commercial market that has been built up so carefully over the years in Tanzania. "It's all your eggs in one basket," says Lengeler. "If the government plans a mass campaign and it doesn't happen, there is no backup." And if campaigns aren't repeated, he warns, within 3 to 5 years, the country "will go backwards. Nets are destroyed or lost, new babies are born, and it happens fast."

With Tanzania's application for continued support due to the Global Fund in July, the partners settled on a middle ground: They would continue giving out the vouchers but increase their value so that the maximum a woman would pay would be 40 cents per net. They would also switch to the more expensive long-lasting nets, which cost about $5 each. And in 2008, they would launch a massive catch-up campaign to give a free net to each child younger than 5.

Sachs, however, wasn't impressed. When he jetted into Dar es Salaam for 2 days in July, he tried to convince the president and the minister of health to change course and rewrite the proposal. In a series of e-mails and phone calls before and after his visit, Sachs blasted the Tanzanian plan in general and Lengeler in particular. Tanzania is being encouraged to be bold, and Lengeler is standing in the way, Sachs wrote to one of Lengeler's colleagues. He called Lengeler's defense of the current system "shocking" and "reactionary." In an e-mail to Lengeler, Sachs dismissed his approach as "disreputable" and "economically ignorant."

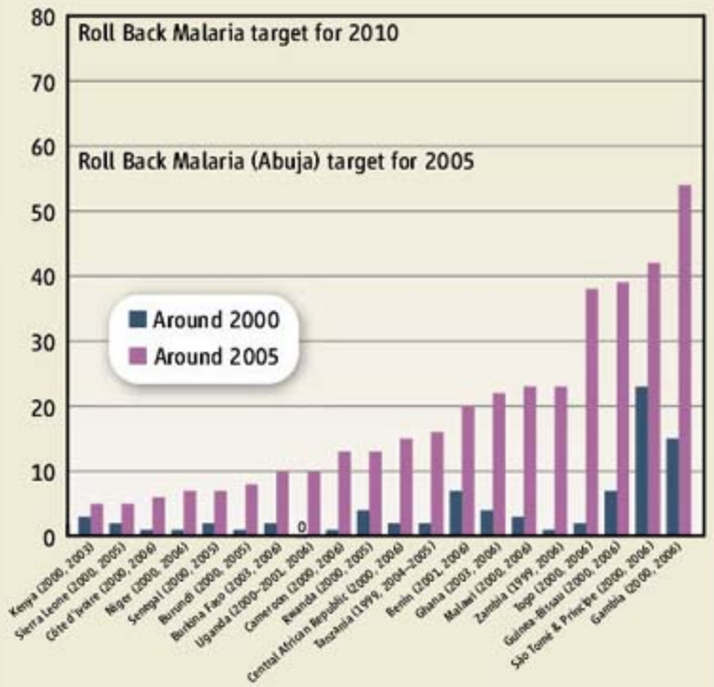
"Jeff Sachs is entitled to his opinion," responds Alex Mwita, the National Malaria Control Program manager in Tanzania's Ministry of Health. But he denies that Lengeler blocked anything. "No partner was interfering. It is the government that makes policy." And the priority is clear, he says: Get nets out fast, whichever way works best.

> **"There is no universal one-size-fits-all solution to malaria."**
>
> —Christian Lengeler, Swiss Tropical Institute

Mwita adds that he is all for universal coverage: "Everyone deserves to be protected … if we have the resources," he says. "We would need $200 million for universal access in Tanzania. That is almost three-fourths of the Ministry of Health budget. The government doesn't have that much money. Bill Gates can give it. Or Warren Buffet can. … But you can't depend on Bill Gates and Warren Buffet always." Until such funding is assured, Mwita says Tanzania will continue to focus its efforts on getting bed nets to children who are most at risk of dying.

And so the debate continues, with more commentaries in various journals and more phone calls between Sachs and Tanzania's president. The Tanzanian Ministry of Health submitted its proposal as written, although at Sachs's urging, it is now drafting a new proposal for a free mass campaign in 26 of Tanzania's hard-hit districts. Sachs, who is pushing for a nationwide campaign and says he has the president's support, has vowed to find money for it. Meanwhile, Sachs has continued to rebuke the skeptics on the global stage.

Progress, But a Long Way to Go



Percentage of children under age 5 sleeping under an insecticide-treated bed net, sub-Saharan Africa, 2000–2005

SOURCE: UNICEF; CREDIT: COURTESY OF CHRISTIAN LENGELER

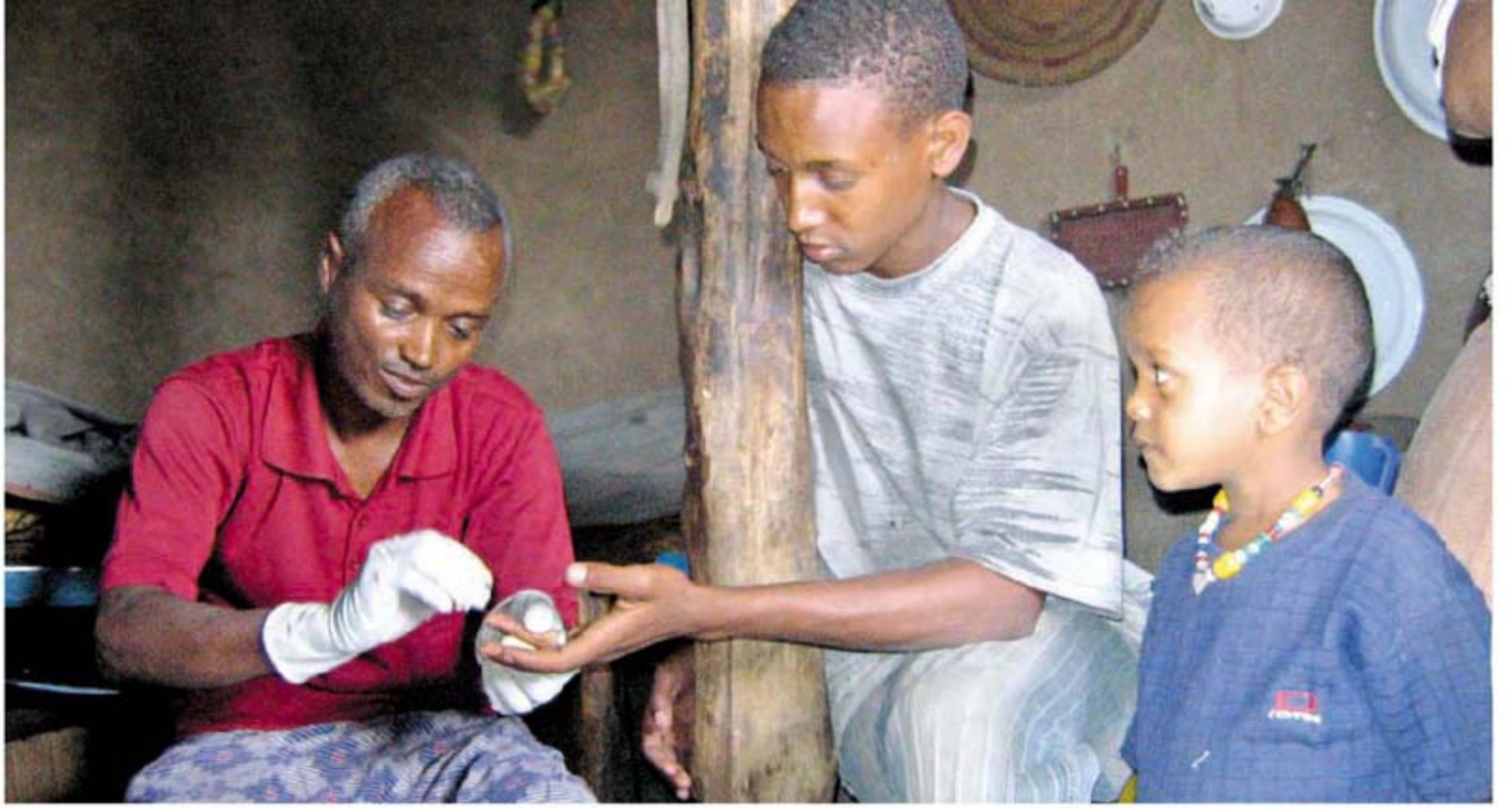
Resolution?

Grabowsky is optimistic that the feuding factions will coalesce eventually, if not this year, around a game plan for getting bed nets out fast to most, if not all, of the population. And there is still a long way to go. A recent study estimated that as many as 264 million nets are needed just to reach the Abuja goal—80% coverage of vulnerable groups—much less fulfill Sachs's vision of universal coverage.

There will need to be catch-up and keep-up strategies, says Grabowsky, and to date, few countries have managed to implement both. There is probably room for multiple approaches, even vouchers and the commercial sector, he suggests. He says the Global Fund is "agnostic" on which approach countries should take; its strategy is to fund those programs that seem to have the best chance of working on the ground. And right now, there are lots of experiments but few definitive answers, he says.

As for the intensity of the debate Sachs has ignited, Grabowsky says, "at its best, public health is a public process. We are all better off having a vigorous debate. There was a time when few people cared about Tanzania's malaria problem. Now we all do."

–LESLIE ROBERTS



Malaria Treatment: ACT Two

An influx of money and a new generation of drugs called artemisinin-based combination therapies (ACTs) are raising optimism that malaria's toll can be reduced

KUNKURA KEBELE, ETHIOPIA—Fanta Dargie and his family live in a modest mud hut, furnished with little more than a table, a few chairs, two hammocks, and some shelves holding the basic necessities for life in Ethiopia's poor countryside. And yet, he's on the forefront of a medical revolution.

Hidden in a corner on the dusty floor of Dargie's hut, in a hamlet 450 kilometers north of Addis Abeba, is a white box the size of a photocopier. After opening a minuscule padlock, Dargie shows the contents: blister packages containing the latest generation of malaria drugs. Rummaging through the box, he also pulls out dozens of simple diagnostic tests, each smaller than a cigarette lighter, as well as rubber gloves, some pens, and meticulously filled-out patient forms.

Every morning before Dargie goes to work, people from his and surrounding villages can come see him if they, or their children, have a fever. He will draw a drop of blood and test it for the presence of *Plasmodium falciparum*, the deadliest malaria parasite, a procedure that takes just minutes. If the test is positive, he can immediately give the patients free pills to take home, along with simple instructions on how to use them.

Dargie, a farmer who volunteers as a "community health worker," knows all about the importance of the drugs distributed in this study. He lost two children to malaria. "I don't want that to happen to other people," he says.

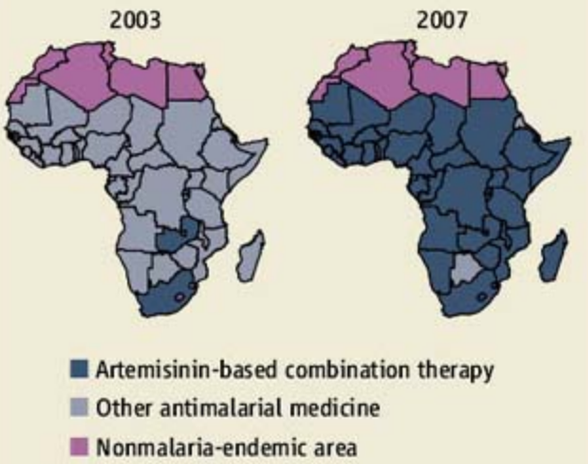
Many people ask why it has taken so long. The new generation of drugs, called artemisinin-based combination therapies (ACTs), has been around for a decade. They're effective and easy to use, and they cost less than $2 for a potentially lifesaving 3-day treatment course. And yet, a shortage of money, a lack of political will, and logistical problems have long prevented the drugs from reaching those who need them—especially in Africa, where malaria kills an estimated million people a year.

Not any more. Money to buy the drugs has started pouring in through agencies such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Affected countries have become serious about introducing ACTs, and they are coming up with new ways—such as the pilot project Dargie is participating in—to bring them almost to the patient's doorstep. These fine-grained distribution systems are a logistical puzzle—but they're crucial, because a child can die from malaria within 24 hours of the onset of the first symptoms. Meanwhile, an unprecedented new plan to serve private markets through a "global subsidy" may see the light of day next month.

This new push to introduce ACTs—along with the massive distribution of insecticide-treated bed nets (see p. 557)—is giving many malaria fighters hope that, after years of failures and broken pledges, they may finally be on the cusp of making a significant dent in the disease's toll. The experience in places such as Zanzibar, where new data suggest malaria transmission has collapsed, has given them hope that results may come fast as well.

"We do get real, perceptible, stunning results," says Kamini Mendis of the World Health Organization (WHO) in Geneva, Switzerland. "I really think we are in a good position now," adds Nicholas White, a malaria

Changing Policies



Country recommendations for first-line treatment of uncomplicated malaria, 2003 and 2007.

CREDIT: M. ENSERINK/SCIENCE; SOURCE: UNICEF

On the front lines. Fanta Dargie, a community health worker in rural Ethiopia, demonstrates a rapid diagnostic test for *Plasmodium falciparum*.

researcher at Mahidol University in Bangkok, Thailand, who has long battled to get ACTs introduced.

An old new weapon

Artemisinin is a compound derived from *Artemisia annua*, or sweet wormwood, a plant that has long been known to help fight fever in China. After groundbreaking Chinese studies in the 1970s, the compound made its way to Western labs in the 1980s. Along with a small slew of chemical relatives, it was found to be highly effective against *Plasmodium*, and despite widespread use, especially in Asia, there have been few signs of resistance in the malaria parasite. To keep it that way as long as possible, experts agree that the drugs should always be taken with another, existing malaria drug. Hence the combination therapies.

But as the evidence of their efficacy grew—and older drugs such as chloroquine and sulfadoxine-pyrimethamine became increasingly useless—patients still weren't benefiting. "I think we were naive to think that evidence would naturally translate into new policies," White says. "It does in rich countries. But in Africa, mothers who lose their child don't come banging on the doors of Parliament."

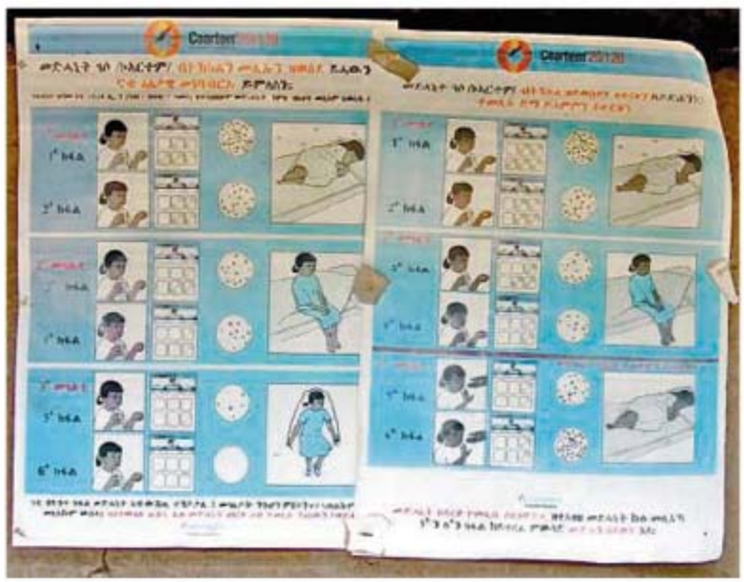
Money was long a key problem, but so was institutional inertia. Compared with older drugs, which cost a dime or less per treatment course, the cost of ACTs was prohibitive for many African governments. Although WHO officially started advocating ACTs in 2001, it didn't push hard enough for the switch, says White.

A vast partnership called Roll Back Malaria (RBM), launched to much fanfare in 1998, also proved a disappointment. Comprised of almost every organization or agency involved in malaria, RBM went through one leadership change after another and ended up in turf battles with WHO; meanwhile, a set of ambitious targets set in the Nigerian capital Abuja in 2000—including the plan to halve the malaria burden by 2010—were going nowhere. "There was far too much talk, and endless meetings, but no action," White says.

Donor countries and the Global Fund, too, have come under fire for not acting swiftly enough. Leading the criticism has been Amir Attaran, a Canadian law professor and immunologist, who, with others, accused the fund and WHO of "medical malpractice" in an article published in the 17 January 2004 issue of *The Lancet*—a charge that the organizations say was unfair and based on inaccuracies, but which they also recognize as having helped speed change.

Meanwhile, there were problems with the supply of artemisinin as well. The compound is extracted from *A. annua* plants, grown mostly on farms in China and Vietnam that had trouble keeping up with the booming demand. Researchers are working to synthesize the compound or make *Escherichia coli* churn it out (*Science*, 7 January 2005, p. 33), but this is expected to take at least another 5 years.

The landscape looks very different today.



Easy as one-two-three. A pictorial taped to an Ethiopian hut shows how to use a 3-day course of Coartem, an ACT.

Donors are pushing ACTs, and a United Nations Children's Fund (UNICEF) report issued last week showed that all but a few African countries have switched their policies—at least on paper—to make ACTs the standard treatment. Although long-term worries about the artemisinin supply remain, the price has come down sharply. Pharmaceutical companies have started mass-producing four WHO-recommended ACTs, and the Medicines for Malaria Venture (MMV) in Geneva, Switzerland, has three more combinations in phase III clinical trials. Many say RBM is working better since the latest reform, 2 years ago.

But the biggest change has been the increasing political attention and the new money. Few would have predicted 10 years ago that a U.S. president would celebrate Africa Malaria Day—and do a goofy dance with a West African dance company—at the White House, as President George W. Bush did last May. ("I think I made his day by saying the European Union should do the same," says MMV President Chris Hentschel, who attended the event.) The Global Fund is flush with cash, and other funds—such as Bush's 5-year, $1.2 billion President's Malaria Initiative and UNITAID, paid for by a tax on airline tickets in eight countries—have also begun disbursing money.

As a result, more than 100 million ACT treatment courses found their way to patients in 2006, up from just 3 million in 2003. Some 63 million of those were a combination of artemether and lumefantrine, produced by Novartis under the brand name Coartem; the company is making more of it than any company has ever produced of any drug, a Novartis spokesperson says.

That doesn't mean there aren't still major problems. One hundred million is less than one-fourth of the number of malaria treatments taken worldwide every year. And the UNICEF report shows that in 14 sub-Saharan countries for which good data were available between 2004 and 2006, Zambia provided just 13% of febrile children with ACTs; all the others scored less than 6%. (The numbers are expected to be much higher in the next survey.)

Procedures to apply for the drugs through the Global Fund are complicated and lengthy, says Mendis; many countries saw their proposals rejected in the fifth and sixth round of funding. Because countries often apply with integrated control plans, ACT delivery can suffer if, for instance, a country's bed-net strategy is judged insufficient. RBM and other organizations are helping countries put together better proposals for the current, seventh round.

But even when the drugs arrive, the logistics of distributing them are often difficult. Several ways to change that are on display in Ethiopia, where 50 million people live in malaria-ridden areas. The government is in the process of employing 30,000 health-extension workers, who, after a full year of training, visit villages and dispense medicines as well as advice for prevention and family planning. They play an indispensable part in delivering ACTs, says Ethiopia's federal health minister Tedros Ghebreyesus, who also chairs RBM's board. Ethiopia has also earned praise for delivering almost 20 million insecticide-treated bed nets within the past 2 years.

CREDIT: NOVARTIS

The program in the northern province of Tigray in which Fanta Dargie participates goes a step further. Instead of distributing ACTs through clinics or salaried health-extension workers, it uses community volunteers who have received just a few days of training. In this trial, supported by WHO and Novartis, researchers are trying to find out whether distributing ACTs this way is safe, what the effects on morbidity and mortality are, and how many are used, says Asefaw Getachew of the Carter Center in Addis Abeba, who coordinated the trial while at the Tigray Regional Health Bureau.

But many are already convinced that distribution through volunteers will prove the way to go—especially for the rural poor who live too far away from a clinic or health post to take their sick child, says Awash Teklehaimanot, a malaria expert at Columbia University's Earth Institute in New York City who also runs the Center for National Health Development in Addis Abeba. There are concerns about overuse, but the lack of resistance seen so far suggests "that we shouldn't be too conservative," he says. "It's no use hoarding these drugs in health centers when people are dying in the village."

Private business

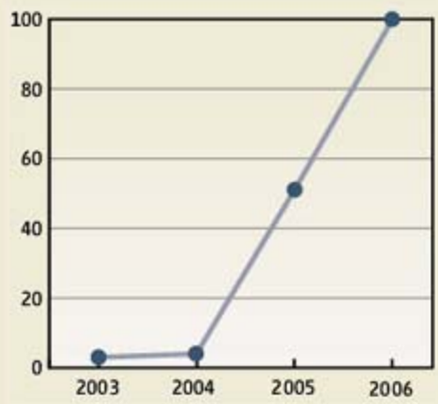
But although many applaud Ethiopia for expanding its health-care system, the private market is a different story, and for now, it's the bigger one. At the moment, some 75% of malaria patients worldwide buy their drugs at a local pharmacy or drugstore, where ACTs, if available at all, are often much more expensive than a bewildering array of older drugs, artemisinin monotherapies, traditional medicines, or counterfeit drugs.

The plan for a global subsidy—although it might also benefit public procurements of ACTs—is hoped to have the biggest impact in this private business. The idea is that consumers will choose ACTs if they cost 10 cents or less; to get there, while still allowing wholesalers and retailers their usual profit margin, a new fund—recently christened Affordable Medicines Facility for malaria (AMFm)—would make a substantial copayment to the producer whenever a wholesale company or government agency decides to buy a shipment of WHO-approved antimalarial drugs. The goal is for the buyer to pay just 5 cents per treatment course—including shipment to the country. The current plan calls for an annual budget climbing to $300 million by 2010; UNITAID has expressed an interest in footing the bill.

First proposed in a 2004 Institute of Medicine report from a group led by economist and Nobel laureate Kenneth Arrow, the idea languished for a while; some worried that a subsidy would line industry's pockets, whereas existing funding agencies felt it threatened their turf, says Harry van Schooten of the Dutch Ministry of Foreign Affairs, which has been pushing the plan. But it gained traction after a January meeting in Amsterdam, and now agencies such as the Global Fund, UNICEF, and WHO are vying to host the AMFm's secretariat, he says. RBM's board is expected to approve the plan at a November meeting.

CREDIT: M. ENSERINK/SCIENCE; SOURCE: UNICEF

ACTs on the Rise



Number of doses of artemisinin-based combination therapies procured worldwide, 2003–2006 (millions).

Still, the devil is in the details, says WHO's Mendis. Dealers may be tempted to charge high prices for ACTs anyway, for instance. "How do we prevent the subsidy from going to the pockets of the middlemen?" she says. Several measures can help prevent that, answers Van Schooten; ACT packages could have a printed price on them, patients will need to be educated, and countries will have to regulate their domestic ACT market and monitor drug quality. Whether African governments are up to that job remains to be seen.

Other concerns remain as well. A stagnating demand for the raw product in 2007 has caused artemisinin prices to drop from a high of $1100 to $1400 a kilogram to about $200 now. At that rate, farmers can make more by planting rice, says WHO's Andrea Bosman, who worries about new price hikes and shortages in 2008. And although the lack of resistance to ACTs is encouraging, that is probably just a matter of time, and new drugs need to be developed rapidly, says Ghebreyesus. "What's plan B? We don't have alternatives at the moment," he says.

Toward eradication?

But these concerns can't dampen the sense of optimism in the air for the first time in many years. Whether that means Abuja's goals can still be met is under dispute. Attaran—who does concede major progress—believes far too much time has been wasted for that. Former Senegal health minister and RBM executive director Awa Marie Coll-Seck asserts they're still achievable—or at least in some countries. So does Teklehaimanot, who coordinated a Millennium Project working group that proposed setting an even more ambitious goal: a 75% reduction from the 2005 level in 2015.

The truth is that we may never know for sure, says Mendis. Malaria mortality can only be estimated because many patients die at home without being counted, and although much is being done to strengthen data collection, there are few baseline data for 2000 on which claims of success could be based.

But things such as bed-net and ACT coverage can be measured more easily, and where they have shot up, malaria rates appear to be dropping encouragingly fast, she says. In Zanzibar, for instance, where ACTs and bed nets were widely introduced from 2004 on, cases had dropped by almost 90% in the first half of 2006. São Tomé and Príncipe, a small island nation off Africa's West Coast, has also seen its rates plummeting, says Teklehaimanot. In Ethiopia, malaria now accounts for 10% of deaths, compared with 25% a few years ago, says Ghebreyesus.

Those developments—as well as encouraging reports from vaccine trials—have even brought back a word last heard in the 1960s in the context of malaria: eradication. "To aspire to anything less is just far too timid a goal for the age we're in," Melinda Gates, who, with her husband, Bill, has invested billions in the malaria battle, said last week at a meeting in Seattle, Washington.

But others say it's much too early to talk about that. For White, all the newfound optimism is cause for a new worry: What if the fight is so successful that politicians and donors lose interest? "We better get prepared for the next phase," he says, "because there will be a lot of good news in the next few years."

–MARTIN ENSERINK

LETTERS

edited by Jennifer Sills

Retraction

IN A PAPER TITLED "VISFATIN: A PROTEIN SECRETED BY VISCERAL FAT THAT MIMICS THE EFFECTS of insulin" (*1*), we identified a protein that is secreted by visceral fat of humans and mice and named it "visfatin." The same protein had been identified previously by other laboratories as "pre-B cell–colony enhancing factor," a cytokine that is expressed by lymphocytes (*2*) and that displays nicotinamide phosphoribosyltransferase activity (*3*). In the *Science* Report, we investigated visfatin's metabolic effects and the biochemical mechanism by which it might exert these effects. We showed that visfatin induces adipocyte differentiation in vitro and that plasma levels of visfatin correlate with visceral fat mass in humans. We also showed that male mice with only one functional copy of the visfatin gene have modest elevations in plasma glucose and that adenovirus-mediated delivery of the visfatin gene to c57BL/6J or KKAy mice resulted in a lowering of plasma glucose and insulin levels. Finally, we reported that visfatin binds to and activates the insulin receptor and we speculated that its activity as an insulin mimetic might explain its metabolic effects.

The visfatin work performed in our laboratory was recently investigated by the Committee for Research Integrity (CRI) of Osaka University Graduate School of Medicine. On the basis of the CRI report, which focused largely on our biochemical experiments examining visfatin's interaction with the insulin receptor, the Faculty Council of Osaka University Medical School recommended that we retract the entire paper. At the suggestion of the Editor of *Science*, we have agreed to retract the paper, even though we continue to stand by our conclusions. We note that over a dozen subsequent publications have shown that plasma visfatin levels in humans correlate with various metabolic states, including obesity, visceral fat mass, and diabetes [for example, (*4*–*6*)]. We note also that another laboratory recently reported that visfatin has insulin mimetic effects in cultured osteoblasts (*7*). We acknowledge that, since publication of the *Science* Report, we have found that not all preparations of visfatin bind to and activate the insulin receptor. Thus far, we have found four different lots of purified recombinant visfatin protein that have both adipogenic and insulin mimetic activities. We still have the preparations of visfatin that show insulin mimetic activity, although the amount is limited, and we are willing to send them to other investigators for independent validation. We are continuing to investigate the significance of this molecule.

We regret any inconvenience caused by this retraction to researchers and readers. The corresponding author is responsible for the retraction.

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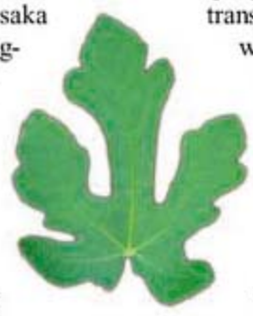
Borrowing from Biology

AS TWO BIOLOGISTS, WE OFTEN MARVEL AT the way humans solve problems by adapting approaches that nature developed eons earlier. A classic example might be our 20th-century discovery of genetic engineering. In plant crown gall disease, a lowly bacterium long ago evolved a highly effective transformation vector (Ti plasmid), which efficiently engineers the plant to produce "food" to the bacterium's order. Much of plant genetic engineering is now based on the same vector system.



The recent News of the Week article by E. Kintisch, "Light-splitting trick squeezes more electricity out of Sun's rays" (3 August, p. 583), seems to be another wonderful example of this sort of "coincidence." In plant photosynthesis, a network of pigment molecules forms a light-harvesting antenna that absorbs photons of varying wavelength and transfers the energy to the pigment molecule at the reaction center. As is often the case, nature is somewhat more sophisticated than the approach described in the recent paper, but the idea is the same: Energy of different wavelengths is captured to avoid waste. Perhaps we should study biology more often and more directly for solutions to our pressing "modern" problems.

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CREDIT: PHOTOS.COM

Counting on Embryos

THE UNDERLYING DATA IN THE POLICY FORUM "Willingness to donate frozen embryos for stem cell research" (A. D. Lyerly and R. R. Faden, 6 July, p. 46) are unclearly characterized, poorly detailed, and questionably analyzed. The description of the study as a "national survey" implies that it is a nationally representative survey, based on a probability sample drawn via accepted survey research practices. Instead, we are presented with a nonrandom convenience sample of nine clinics. The selection procedure used to choose the clinics, and to choose the patients within each clinic, remains undisclosed (contrary to the disclosure principles of the National Council on Public Polls and the American Association for Public Opinion Research). The authors extrapolate their nonprobability data to estimate a national incidence of available embryos, with no discussion of the limitations of this approach. Convenience samples in studies of biological functions are common; a probability sample is not necessary to demonstrate that a sharp stick in the eye hurts. Attitudinal research, such as this study, is not afforded this luxury. These circumstances are noteworthy, given that the initial release of this article—in your online edition the same day as President Bush's latest veto of stem cell research legislation—seemed timed to influence the public discourse [e.g., (*1*)]. Broader disclosure and more circumspect use of convenience samples in attitudinal research are advisable, particularly for a publication of *Science*'s stature.

GARY LANGER
Director of Polling, ABC News, 7 West 66th Street, 7th Floor, New York, NY 10023, USA.

Reference
1. S. Kliff, "The donors have spoken," Newsweek.com, 20 June 2007; www.msnbc.msn.com/id/19339342/site/newsweek/.

Response

LANGER'S CRITIQUE MISCONSTRUES BOTH the methodology we used and the conservative character of our estimate of the numbers of cryopreserved embryos that might be available for research. Ours was not a national opinion poll and never aspired to be. The methodology of public opinion polling, with its focus on national probability sampling, is inappropriate for research on clinical populations, regardless of the nature of the study.

Unlike existing research on infertility patients' preferences for and experiences with the disposition of cryopreserved embryos, which have largely come from a single clinical site, we were able to recruit patients from nine different clinical settings, both academically affiliated and private in regionally diverse locations across the United States. At each of these clinical settings at least 50% of the respondents with embryos in storage indicated they were somewhat or very likely to donate them to stem cell research.

Our estimate of the number of embryos that might be available for research is reasonable, for several reasons. First, we used a 2001 estimate of the number of cryopreserved embryos in the United States; given the industry's growth in the past six years, there are likely more than 400,000 embryos in cryostorage today. Second, across the entire sample, 60% of the respondents indicated that they were somewhat (21%) or very (39%) likely to donate cryopreserved embryos for stem cell research, but we assumed that only 50% would ultimately be willing to donate, giving us 200,000 potentially available embryos. We then reduced this number again by 50%, on the assumption that as

many as half of these embryos would be used for reproductive or other purposes, leaving us with 100,000 embryos that our data suggest might be available for research.

More to the political point, prior to our report, the only existing attempt to estimate the availability of embryos for research in the United States, which was made based on the reports of infertility clinics—rather than infertility patients—had placed the number at less than 3% (*1*). Our data, which represent an attempt to introduce the perspective of infertility patients into this debate, provide a solid basis for concluding that this estimate is way too low and that, once their reproductive projects are completed, many infertility patients prefer donating their cryopreserved embryos to research over making them available for adoption or allowing them to be thawed and discarded.

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Modified Newtonian Dynamics Close to Home

IN HIS PERSPECTIVE "SEEING THROUGH DARK Matter" (3 August, p. 607), Stacy McGaugh describes the success of a modified Newtonian dynamics (MOND) in explaining the flat rotation curves of galaxies without invoking dark matter. In addition to noting that MOND is in accord with available data and observations, it is possible to directly test Newtonian dynamics in the laboratory, even at low accelerations. This has recently been done in a test of Newton's second law ($F = ma$), and perfect agreement with Newton was found down to accelerations of 10^{-13} m/s^2, three orders of magnitude below the scale at which MOND should set in (*1*). Similarly, Newton's gravitational law has been tested to very small accelerations (i.e., with very small masses at small distances), and no deviations from the law were needed to describe the solar system (*2*). Thus, while no observational data disagree with MOND, recent laboratory tests indicate that Newtonian dynamics also explain galaxy rotation curves and apply to accelerations in the galaxy tails.

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2. J. Ciaverini *et al.*, *Phys. Rev. Lett.* **90**, 151101 (2003).

Response

CHRISTOF AEGERTER RIGHTLY POINTS OUT that no deviations from purely Newtonian behavior have been detected in the laboratory (*1*) to accelerations lower than the critical acceleration scale of MOND, where the mass discrepancy becomes evident in galactic systems. While a laboratory test of MOND would be highly desirable, Grundlach *et al.* (*1*) themselves point out that their result does not provide such a test. The reason is that their laboratory sits on the surface of the earth, where the acceleration we feel is 11 orders of magnitude above the MOND scale. It is the total acceleration that matters in MOND, so terrestrial experiments always exhibit Newtonian behavior even if their internal accelerations are arbitrarily small.

A proper laboratory test of MOND requires that the apparatus itself be located in a region of very low acceleration, an extraordinarily difficult situation to arrange (*2*) on Earth. How far from Earth we need to be to detect MOND effects depends on the sharpness of the transition between the Newtonian and MOND regimes. In the optimistic case of a gradual transition, the Pioneer anomaly (the deviation of two Pioneer spacecraft in the outer solar system from their predicted trajectories) (*3*) might be a MOND effect (*4*, *5*). Other solar system constraints (*6*–*8*) appear to favor a sharper transition, and the natural location for a clean experiment would be deep in intergalactic space. While that is obviously impossible, real laboratory tests are feasible. For example, in the relativistic extension of MOND hypothesized by Bekenstein [the tensor-vector-scalar gravity theory (*9*)], strong MOND effects are anticipated in regions where the gravitational potential nears zero. Such cancellation can be found at a point between the Sun and Earth (*10*), so a critical test is achievable with an appropriate satellite experiment.

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Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

CORRECTIONS AND CLARIFICATIONS

Table of Contents: (28 September, p. 1825). The author names were omitted from the Report titled "Genomic minimalism in the early diverging intestinal parasite *Giardia lamblia*." The authors of this Report are Hilary G. Morrison *et al.*

Reports: "The Slit receptor EVA-1 coactivates a SAX-3/Robo–mediated guidance signal in *C. elegans*" by K. Fujisawa *et al.* (28 September, p. 1934). SLT-1 was mistakenly defined as "Shiga-like toxin 1" in the first sentence of the abstract and in the third sentence of the first paragraph of the text. The corrected sentence in the abstract should read "The SAX-3/roundabout (Robo) receptor has SLT-1/Slit–dependent and –independent functions in guiding cell and axon migrations." The corrected sentence in the first paragraph should read "One such mechanism involves the SLT-1/Slit guidance cue, a large secreted protein with several predicted N- and O-glycosylation sites (*2*), and its receptor SAX-3, a homolog of the transmembrane (TM) roundabout (Robo) receptor (*3*–*6*)."

ScienceScope: "China's spending boom" (21 September, p. 1663). The data on China's research budget refer to 2006, not 2007.

Random Samples: "Monkeys have tin ears" (3 August, p. 577). The photograph mistakenly showed a chimpanzee instead of a monkey.

Reports: "Quantitative imaging of nitrogen fixation by individual bacteria within animal cells" by C. P. Lechene, Y. Luyten, G. McMahon, and D. L. Distel (14 September, p. 1563). Claude Lechene should be the only corresponding author listed. The asterisk beside Daniel Distel's name on p. 1563 and his e-mail address on p. 1564 should be deleted.

HISTORY OF SCIENCE

An Alternative Synthesis

Ron Amundson

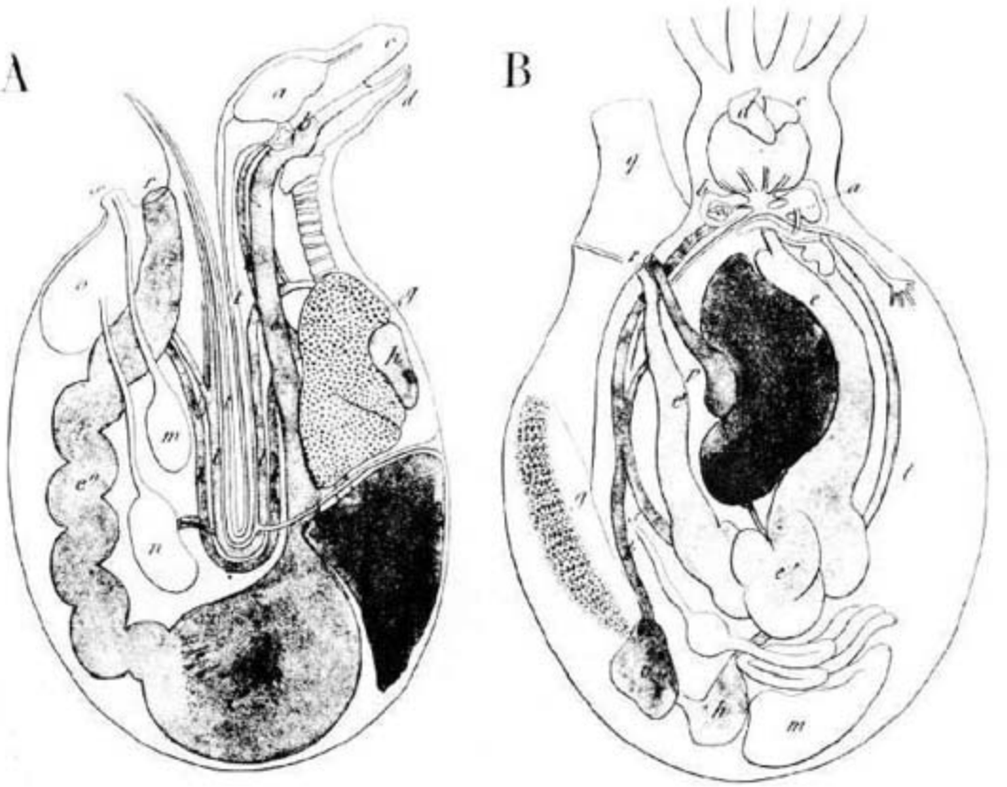
From Embryology to Evo-Devo presents a collection of papers by historians, philosophers, and biologists that were discussed at a Dibner Institute workshop in the fall of 2002. It immediately brings to mind a similar work, *The Evolutionary Synthesis* (*1*). This pair of edited volumes, appearing a quarter-century apart, offers an almost yin and yang of the history of evolutionary thought. Most 19th-century evolutionists saw embryonic development as central to the evolutionary process. The contributors to the 1980 volume edited by Ernst Mayr and William Provine viewed it as essentially irrelevant. (Although, as the newer volume shows, many strands of developmental evolutionary thought persisted during the heyday of the modern synthesis.) Evo-devo brings the developmental view of evolution back to the fore.

From Embryology to Evo-Devo
A History of Developmental Evolution
Manfred D. Laubichler and Jane Maienschein, Eds.
MIT Press, Cambridge, MA, 2007. 577 pp. $55, £33.95. ISBN 9780262122832.
Dibner Institute Studies in the History of Science and Technology.

The only author to appear in both volumes is historian Frederick Churchill. In 1980, he reported a crucial fact about 19th century biology: "Heredity" was then understood as an aspect of embryonic development itself. It was the process by which similar traits developed within both parents and offspring. Evolution obviously involves heredity, and so the interweaving of development and heredity implied an interweaving of development and evolution. The conceptual separation of heredity from development was achieved by T. H. Morgan and his associates. Transmission genetics became the new "heredity," carved free of development. Only then was evolution easily conceived as independent of development. Churchill claimed that the separation of development from heredity was "fundamental to the formation of modern biology." It certainly was fundamental to the evolutionary synthesis. Transmission genetics begat population genetics, which begat the modern synthesis. At no step along the way was development relevant to evolutionary change (*2*). Most contributors to Mayr and Provine described the then-60-year history of the evolutionary synthesis as utterly separate from embryology and from related fields, such as comparative morphology and versions of systematics that emphasized higher taxa.

In the 2007 volume, edited by Manfred Laubichler and Jane Maienschein, Churchill takes a subtly different stance toward the bifurcation of development and heredity. He discusses the refutation of the biogenetic law by 19th-century contemporaries of Ernst Haeckel. The results were the research programs in evolutionary embryology of such figures as Francis Balfour, Eugen Korschelt, and Karl Heider. These biologists took account of embryonic causation and adaptation, not only the appearances of recapitulation. Churchill observes that their programs show many similarities with evo-devo. This theme is taken up many times in the Laubichler and Maienschein volume. Some chapters address relations among research traditions: for example, Scott Gilbert discusses fate mapping, cell lineage studies, and the relation of these fields to modern gene expression maps. Other chapters focus on individual researchers, either from before the synthesis (e.g., Balfour and William Bateson) or from the era in the 20th century when it held sway (e.g., Dwight Davis, John Tyler Bonner, and Rupert Riedl).

I couldn't help but wonder where this new perspective leaves the bifurcation of heredity from development. If evo-devo turns out to be the success that its advocates are envisioning, perhaps we will witness a breakdown of the heredity-development dichotomy. Recent discussions of what is now called "epigenetics"—a field that centers on development—have come very close to saying that it simultaneously involves heredity (*3*). Philosopher James Griesemer's chapter addresses this issue, beginning with Gregor Mendel and August Weismann. These are the two 19th-century heredity theorists usually thought to be most "modern," in the Churchillian (1980) sense of conscientiously separating heredity from development. According to Griesemer, this is an error. Mendel and Weismann shared the assumptions of their contemporaries; heredity was an aspect of development. He goes on to argue that transmission genetics



Differ by inversion? Étienne Geoffroy Saint-Hilaire claimed that all animals share a fundamental body plan and suggested a dorsoventral inversion between vertebrates and invertebrates. To ridicule such comparisons among body plans, Georges Cuvier drew roughly comparable arrangements of organs in a duck folded on its back (**A**) and a cephalopod (**B**). He argued that there are far more differences than similarities [from (*5*)].

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itself is a study of development. It must be the study of development in the sense that the study of cooking "must be" the study of chemistry. (Chefs may deny that they are studying chemistry, but chemists know better.)

One underlying message of many of the chapters is that historical attempts to explain evolution in terms of development were productive but incomplete (contra *The Evolutionary Synthesis*). Evo-devo is a promise for their completion. (The historians tended to avoid this presentist bias, but philosophers and scientists found it nearly irresistible.)

One weakness in the presumption of continuity between historical theorists and modern evo-devo is the current prominence of the comparative molecular mapping of gene expression. That field is crucial to evo-devo. As Gilbert's chapter points out, it "brought the notion of structure back into developmental biology." Without the centrality of organic structure, any similarities between the centuries are superficial. But as informative as it is, gene expression mapping is analogous only to a narrow range of historical precursors, comparative embryology and morphology (scarcely more than what Ernst Haeckel considered). These fields do not yield mechanistic explanations of evolutionary change. If evo-devo is to fulfill its promise, it must go beyond comparison and provide causal details of the actual changes in ontogeny by which new forms were evolved.

Such causal details are often claimed to be viable goals for evo-devo explanations of evolutionary innovations and novelties (discussed in the chapters by Alan Love, Gerd Müller, and Günter Wagner). What we now call innovation and novelty was previously studied under the rubric of "origins of higher taxa": such as the neural crest characterizing vertebrates and the fin-limb transition for tetrapods. Some argue that evo-devo has greater potential to explain novelties than the modern synthesis had because population genetics can only deal with modifications of structures that already exist (e.g., in terms of preadaptation). Evo-devo has theoretical access to the causal processes of embryogenesis, which can potentially explain the origins of genuinely novel structures. Innovations are not merely modifications of old structures, but new products of modified ontogenies.

However, Wagner cautions against too much optimism. He recalls the breakdown of evolutionary embryology around the turn of the 20th century. Its advocates had expected to solve the evolutionary problem of form by studying comparative morphology and embryology (with a bit of experimental embryology thrown in). But practitioners could not agree on methodology. The relative importances of embryological and adult morphologies, embryonic adaptations, and causal processes within the embryo were all at issue. The field reached a stalemate by the early 20th century. Wagner believes that evo-devo might suffer the same fate.

But won't molecular biology save us from that fate? Maybe, maybe not. Do we have a principled way of deciding whether the large differences in Hox gene organization between major groups point toward an ancient saltationist cause of evolutionary change (in duplications of Hox clusters, for example) or reflect a later built-up by-product of gradual microevolutionary changes (*4*)? Wagner argues that we may never be able to know the genuine mechanisms by which ontogenetic changes occurred; they may have been too ephemeral to have left evidence. If this is the case, evo-devo will not fulfill the promise of its 19th-century precursors but instead recapitulate their failures.

But it hasn't so far. Like all good history, the studies in *From Embryology to Evo-Devo* give a perspective on the present as well as the past. The same is true when we reread *The Evolutionary Synthesis*.

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PHYSICS

Relativists, Skepticism, and Waves

Michael D. Gordin

Gravitational waves are simultaneously a hot topic and a matter of no interest. On the one hand, the U.S. National Science Foundation (among others) has paid out enormous funds for the Laser Interferometer Gravitational-Wave Observatory (LIGO), which is expected to provide the first concrete evidence of the existence of these waves coursing across the fabric of space-time. You don't get that kind of funding unless there is something to be found and that something is quite important. On the other hand, essentially nobody doubts the outcome of LIGO's work. Although they have never been unambiguously detected, gravitational waves are simply assumed to exist—they are now seen as required by Albert Einstein's general theory of relativity—and LIGO will only put the icing on a cake physicists consumed a long time ago.

Traveling at the Speed of Thought
Einstein and the Quest for Gravitational Waves
by Daniel Kennefick
Princeton University Press, Princeton, NJ, 2007. 333 pp. $35, £19.95. ISBN 9780691117270.

Or so one would think, talking to contemporary gravitational physicists (often called "relativists," without the rancor scientists direct toward historians of that stripe). The great achievement of Daniel Kennefick's fascinating *Traveling at the Speed of Thought* is that he takes this assumed existence of gravitational waves apart. He is not out to show that they do not exist—far from it. Rather, he carefully explains how durable skepticism has been toward the existence of gravitational waves ever since Einstein first predicted them in 1916. Even Einstein was a sometime skeptic, and many of his direct collaborators maintained severe doubts after his death. Yet gravitational waves are now taken for granted. Kennefick tells us how this common sense emerged.

This is no mean feat, considering how complicated the physics of general relativity is, and how hard it is to perform the calculations that predict the existence and behavior of the astonishingly weak gravitational waves. To one extent, then, Kennefick offers a readable (although at times overly technical) account of the theory of gravitational waves, exploring why skepticism was a reasonable stance at various points in the 20th century and why it has ceased to be so in the 21st. This eminently interesting account is, however, the less intriguing aspect of Kennefick's book.

The more interesting aspect concerns the role of analogy in science. Gravitational waves

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Listening for proof. The Livingston Laser Interferometer Gravitational-Wave Observatory, Louisiana.

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provide an almost-perfect case for examining the way analogical reasoning works in science. Analogy proves central in two ways.

The first, more obvious aspect of analogical reasoning in gravitational wave theory pertains to the analogy between electromagnetism and gravity. General relativity posits a field theory of gravity, and Maxwell's equations offer an eminently successful direct analog. The clinching prediction from those equations was the experimental detection of the existence of electromagnetic waves, so to secure relativity one ought to look for gravitational waves. The problem lay in the striking disanalogies between the two forces: gravity is vastly weaker, and it does not possess two opposite charges (mass is its only "charge"). The strength problem makes the waves hard to detect. The charge problem means that there can be no dipole sources of gravitational radiation, and one must begin one's analogies with quadrupole systems (such as binary star systems). Kennefick carefully points out when, how, and why the analogies both produce suggestive results and hopelessly break down.

He is less explicit, however, on the role of analogies within approximation techniques, which are essential to almost every area of theoretical physics. The tensors of general relativity are legendarily complicated to actually compute with, and verifiable predictions can usually be generated only through simplification. These techniques are essentially analogies, in the same sense as the electromagnetic analogy. To take two examples of many such techniques from Kennefick's catalog, the "slow-motion" approximation of Einstein's field equations analogizes them to Isaac Newton's gravitational theory, which is indeed a theory of gravity but excludes the possibility of waves. The "fast-motion" approximation analogizes them to special relativity, which can accommodate the waves but isn't a theory of gravity. Both of these are instances of analogy, and both are essential for the production of useful physics, but they both come with dangers. It is impossible to put down this book without a renewed appreciation for analogical reasoning as a double-edged sword.

Traveling at the Speed of Thought itself bears a doubled-edged character. On the one hand, it is an account of the history of gravitational waves by a one-time student of theoretical physics. The author's closeness to many of the (more recent) actors and to their physical concerns endows the book with much of its passion and vigor. The other edge shows the hallmarks of a historical detective story and shows the payoff of close archival work.

Consider this one example. In 1936, Einstein and his co-author Nathan Rosen submitted a paper to *Physical Review* titled "Do gravitational waves exist?" Einstein and Rosen concluded they did not. *Physical Review* editor John T. Tate somewhat atypically sent out the paper for anonymous peer review, and the referee made important corrections and suggestions that had several effects: Being subjected to review so offended Einstein that he withdrew the paper in a huff and never again published in the journal, and the reviewer's comments forced Einstein to silently correct the mistakes in his work before soon publishing the paper elsewhere. Kennefick provides a virtuoso performance of archival sleuthing and discovers that the reviewer was Princeton relativist Howard Percy Robertson. I leave the detailed story to be enjoyed by the reader but will state that it is not only amusing but offers some real insight into the mind of the world's most famous physicist. Many scientists have had this experience of rage at a peer review. Most scientists pick themselves up and revise the piece to address the referee's concerns. In this, as in perhaps other areas, they are no Einstein.

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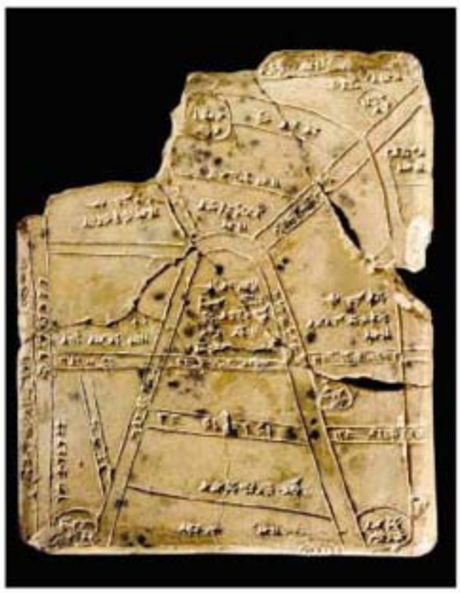
BROWSING

Cartographia. Mapping Civilizations. Vincent Virga and the Library of Congress. Little, Brown, New York, 2007. 272 pp. $60, C$75. ISBN 9780316997669.

This survey across time presents maps (and related images) as primary documents from the exploration of the world: representations of particular places at specific times. Beginning with Babylonia (the source of the cuneiform tablet, *c.* 1500 BCE, showing the plan of fields at Nippur, right) and the Mediterranean, Virga proceeds through Asia, Africa, Europe, and the Americas to Oceania and Antarctica. He concludes with samples of cartographies of culture and science, including depictions of the Internet, the human genome, and literary adventures for children. In addition, the author discusses the stories maps tell about how and why they were made and used.



EPIDEMIOLOGY

Outbreak Investigation and Response Training

Short courses that build skills for investigating and responding to disease outbreaks may enhance response to potential epidemics in resource-limited settings.

Andres G. Lescano,[1]* Gabriela Salmon-Mulanovich,[1] Elena Pedroni,[2] David L. Blazes[1]

The resurgence of poliomyelitis and cholera (*1*, *2*) and the advance of avian influenza (*3*) highlight the need for prompt and accurate response to disease outbreaks. Epidemic events often arise in the developing world (*4*) where countries are less prepared to respond. The World Health Organization's 2007 World Health Report identifies global outbreak response as one of its highest priorities (*4*). Field Epidemiology Training Programs (FETPs) sponsored by the U.S. Centers for Disease Control and Prevention (CDC) have provided training for local epidemiologists, but the need outstrips the programs' availability (*5*). FETPs, which typically provide 2 years of training and mentored field experience (*6*), have led to reduced morbidity and improved public health programs (*7*). However, FETPs are costly (*5*) and take years to implement. We have instead used short, locally targeted courses to build professional capacity for outbreak investigation and response in the Americas.

The Model

The U.S. Naval Medical Research Center Detachment (NMRCD), Lima, Peru, one of the five Department of Defense (DoD) overseas laboratories, developed a 5-day, 40-hour in-classroom course in Spanish aimed at developing skills for disease outbreak investigation and response at Ministries of Health. Training combines lectures, readings, and tutored group work on case studies. Acquired skills are applied by solving case studies and preparing and presenting outbreak reports. Student performance is evaluated with exams, group presentations, and postcourse outbreak reports. The course responds to the context, needs, and diseases of resource-limited settings and has been adapted to various locales and audiences [supporting online material (SOM), p. 19].

Courses are offered on request from the host country. National- and province-level epidemiology units select participants from among those responsible for outbreak-related functions. Courses usually have 30 to 60 students, divided into four to six groups (SOM, p. 2). Faculty members are from NMRCD, the host country, and the local academic community. Courses are accredited by local universities and are often cosponsored by international agencies (*8*). Training is coordinated with available FETPs. All materials are transferred to local faculty to encourage replication and to make continuing education self-sustaining. Course materials in Spanish and English are freely available (*9*).

Outbreak courses taught in the Americas (*8*). Numbers represent trainees per country 2002–06.

After the course, students were asked to report a contemporaneous disease outbreak that required a field investigation, as well as control-and-response measures. Faculty assists with preparation of the reports and provides feedback to graduates. Reports are systematically collected from courses offered by NMRCD (SOM, pp. 2 and 3).

Immediate Outcomes

From 2002 to 2006, 33 courses were taught to 1343 students from 14 countries (see figure, above). In the last five courses, participants included physicians, nurses, biologists, laboratory workers, environmental health specialists, and veterinarians. One-quarter had postgraduate degrees, and 64% were women. Many province-level epidemiology directors and five national directors attended training, as well as FETP trainees in Argentina, Costa Rica, and Peru who registered to reinforce their skills.

About 41% (259 out of 634) of all graduates of 5-day courses taught by NMRCD submitted outbreak reports (samples in SOM). Reported outbreaks were varied, including foodborne and respiratory illness, substance use–related psychosis, Guillain-Barré clusters, and hemorrhagic fever. Although not a representative sample of all outbreaks, this regional compilation is large, diverse, and possibly unique.

Student surveys showed high satisfaction with all course components [mean >4.5 of 5 (SOM, p. 13)]. Pre- and post-tests demonstrated a significant improvement in the average knowledge of concepts and definitions about outbreak investigations methods (SOM, p. 14).

Impact and Sustainability

Course coordinators in Argentina, Costa Rica, and Chile reported that training led to introducing new surveillance, detection, and response procedures, including notification mechanisms, reporting templates, and response teams. They also thought that courses improved their ability to detect, investigate, and respond to outbreaks and stimulated their staff to pursue careers in epidemiology (SOM, p. 16). Additionally, the 84 first graduates who responded to an

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ongoing evaluation reported that they participate in more outbreak investigations after our training (0.2 versus 0.9 investigations per trainee-year, $P < 0.001$). They also reported identifying the source or mechanism of the outbreak more often and publishing more outbreak reports in the scientific literature (SOM, p. 15).

In 4 years, graduates from nine countries have organized 19 replicate outbreak courses, 9 of those without NMRCD support in four different countries (see table, below). The course is now the introductory module of the Argentine FETP and is routinely taught in three Master's degree programs. Graduates of independent and NMRCD courses assumed similar roles after training. One graduate of an independent course became Argentina's FETP field coordinator and has taught in four international courses and has led field investigations in three neighboring countries.

Relationships formed during training resulted in a network of standardized expertise. More than 50 students trained outside their countries to learn the methodology and to bring it home. Peruvian and Argentine faculty also taught in other countries, nurturing partnerships and cross-border coordination.

Host countries shared 25 to 75% of the costs, showing clear interest and commitment. Supported by international agencies and their own funds, countries provide facilities and participant-related costs. NMRCD usually supports course materials and its faculty's salaries and travel (~$2000 for courses in Peru and ~$8500 elsewhere).

Discussion

Outbreak investigation is key for prompt, effective response to health emergencies. Our experience in the Americas demonstrates the feasibility of developing this capacity through a flexible and potentially self-sustaining approach of horizontal partnerships with host countries.

In the Americas, there were only 303 FETP graduates by 2001, and no new programs started since then (*5*), while a mere 24 Latin American epidemiologists graduated from the CDC Epidemic Intelligence Service (*10*). In contrast, our courses produced 1343 graduates since 2002. Four graduates have led national epidemiology units—investigating outbreaks and mentoring junior epidemiologists—both of which are core FETP competencies (*6*). Graduates of both NMRCD and independent courses reached leadership positions in several countries after a few years. Also, outbreak reports addressed important public health issues that required field studies and response measures but had not been formally documented. Outbreak notification became more standardized with the use of NMRCD's templates, which facilitated the continued collection of data and the creation of local outbreak compilations.

Although there are limited data about the value of alternate models (*7*, *11*) and assessing training impact is fraught with methodological challenges, indications of the effectiveness of our program include the following: (i) Course coordinators observed that training improved national detection and response capacities, (ii) graduates reported increased outbreak notification, and (iii) courses were universally well received and frequently replicated.

FETPs offer skills, mentoring, and network linkages that exceed the aims of focused training. Our courses, however, provide skills to design outbreak investigations, to conduct descriptive and analytic epidemiology, and to interpret and present scientific evidence. This structured approach complements the extensive field experience of most participants. Reporting an outbreak in the manner of a scientific manuscript sharpens communication skills and introduces publication practices.

Our approach is made possible by the sustained presence of international research centers in epidemic-prone regions. Centers like NMRCD transfer knowledge and technology, as they accumulate expertise and have mutually respectful relations with host country partners. Also, the location of these centers in high-risk regions reduces travel costs, which allows inexpensive training replication. The CDC Central American Center, the DoD laboratory network, and the Pasteur Institutes also support capacity-building (*12*, *13*) and could replicate our approach in other regions.

Conclusion

Building sustainable response capacity for disease outbreaks in resource-limited settings, as called for by the 2007 WHO report (*4*), is a formidable challenge. FETPs, the gold-standard approach, are often unaffordable because of costs and implementation timelines. More immediate approaches like our outbreak training course may offer viable intermediate steps for many countries to enhance preparedness for future epidemics. As evidenced by how three countries built a cohort of outbreak responders and faculty able to further replicate the training after only two courses, professional capacity can be built incrementally in order to optimize the response to disease outbreaks.

COURSE OUTCOMES

	Peru	Other Countries	Total
No. of courses			
All	13	20	33
Duration (5-day/2-day/half-day)	4/8/1	16/2/2	20/10/3
Spanish/English	12/1	17/3	29/4
Organized by graduates (with NMRCD/independent)	2/2	8/7	10/9
No. of graduates			
All	430	913	1343
Foreign	12	39	51
Trainee performance			
No. of outbreak reports	95	191	286
Students reporting outbreaks* (%)	34.0	44.0	40.9
Attendance (% of enrolled)	91.8	97.7	94.9
Mean overall satisfaction†	4.68	4.70	4.69

*From participants in NMRCD 5-day courses. †Post-course anonymous student ratings (1-to-5 scale, where 5 is best).

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Course outcomes. A growing network of graduates and new courses is established (2002–06) (see SOM).

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NEUROSCIENCE

Maternal Effects on Schizophrenia Risk

Local environmental factors impinging on the fetal brain can tip the balance toward mental illness.

Paul H. Patterson

Understandably, there is great enthusiasm surrounding the search for candidate genes that increase the risk for devastating mental disorders such as schizophrenia. Progress is being made on several fronts, such as identifying genes that regulate potential molecular pathways underlying brain development. Genetic variants are also being associated with brain functions during particular cognitive tasks. What is equally important, though, and at risk of being lost in this gene fervor, is a balanced view of the variety of risk factors for mental illness. Many mental disorders are now referred to as "genetic diseases" as if they were autosomal dominant, like Huntington's disease, in which inheriting a genetic mutation causes the disorder in every person. In the case of schizophrenia, recent epidemiological and animal studies are taking understanding of environmental influences to the molecular level.

Much of the emphasis on the genetics of schizophrenia comes from twin studies, where the incidence of the disorder in genetically identical (monozygotic) twins is 50%. This 50% concordance leaves considerable room for nongenetic influences. However, even that figure may be an overestimate of the role of genetic influence (*1*). Several lines of evidence point to a key role for maternal environment.

Not widely appreciated in deducing the importance of genes from twin studies is the fact that two-thirds of monozygotic twins share a placenta, which is a key environmental factor. Individual placentas vary with respect to the transport of various nutrients and hormones (*2*), which affects normal development. Interestingly, X-chromosome inactivation is affected by placental status (*3*) and, in the largest study of its kind, so is IQ (*4*). It is therefore possible that the placental environment can influence the expression of genes that are linked to neurodevelopment and schizophrenia. Moreover, indirect evidence suggests that monozygotic twins sharing a placenta have a higher concordance for schizophrenia than monozygotic twins with separate placentas (*5*, *6*). It would be extremely informative to directly assess placental status in twin studies of schizophrenia, and there are twin registries where this could be done (*7*).

Placental status could also influence fetal responses to infectious agents in the mother. For instance, twins sharing a placenta are bathed in the identical blood supply of cytokines that are induced by maternal infection. Moreover, sharing a placenta increases the risk for infection in twins (*8*). Birth in winter or spring months, when respiratory infections are frequent, is a well-established risk factor for schizophrenia, and most ecological studies of influenza report an increased incidence among offspring born to mothers who were in the second trimester of pregnancy during an epidemic (*9*). Most importantly, a recent prospective study found that maternal respiratory infection increases the risk for schizophrenia in the offspring three- to sevenfold. Because of the high prevalence of influenza infection, Brown *et al.* estimate that 14 to 21% of schizophrenia cases would have been prevented if maternal infection had not occurred (*9*). Moreover, there is an association between elevated concentrations of cytokines or antibodies to influenza antigens in maternal serum and the incidence of schizophrenia in offspring (*9*). Maternal infection may also play a role in the pathogenesis of autism (*10*), although more epidemiology is needed here. Such links are remarkable, considering that elevated risk may only be in genetically susceptible individuals. If so, the risk associated with maternal infection in that subgroup would be considerably greater than three- to sevenfold.

The maternal environment. Alterations in fetal brain development, and their associated behavioral changes, have been linked to the placental environment in human and animal studies. Image is a color mezzotint from Gautier D'Agoty, *Anatomie des parties de la génération de l'homme et de la femme* (1773).

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Although epidemiological studies cannot establish causality, recent work with animals provides experimental evidence that maternal respiratory infection can influence the physiology, behavior, and neuropathology of adult offspring. For instance, maternal influenza infection in rodents causes abnormal behaviors in adult offspring that are consistent with those seen in schizophrenia and autism. These include deficits in social interaction, working memory, prepulse inhibition, and latent inhibition. The latter deficits display postpubertal onset and are normalized by antipsychotic drug treatment. Maternal infection in rodents is also associated with elevated anxiety and neuropathology in offspring that is consistent with that observed in schizophrenia (*11*, *12*).

Changes in the behavior and neuropathology of the rodent offspring are also elicited by injection of synthetic double-stranded RNA into the mother, which evokes an antiviral-like inflammatory response (*12*–*14*). Molecular manipulation in this model shows that behavior of the adult offspring results from the balance of pro- versus anti-inflammatory cytokines produced by the mother. That is, blocking pro-inflammatory interleukin-6 or increasing the concentration of anti-inflammatory interleukin-10 strongly attenuates the effects of maternal immune activation on fetal brain development (*15*, *16*). Similar findings have been reported for a model in which

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maternal bacterial infection is mimicked in rodents by injection of lipopolysaccharide, an immunogenic bacterial component (*17*).

Although a genetic element clearly contributes to schizophrenia and other mental disorders, the maternal-fetal environment must also be taken into account. Environment can alter genetic outcomes and vice versa, and future research must both tease the two influences apart and consider them together to better understand the onset, progression, and treatment of mental disorders.

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ECOLOGY

Thinking Long Term

Thousand-year records of animal population patterns and climate yield insights into the impacts of environmental change.

Robert A. Cheke

Ecologists seeking patterns in populations and environmental correlations dream of coming to grips with lengthy data sets. Usually, animal numbers are determined both by density-independent environmental factors and by density-dependent population processes involving time lags. Disentangling these different factors requires painstaking fieldwork and mathematical skills from the scientists and the patience of Job among funding agencies. Two new analyses of 1000-year-long data series illustrate how long series can reveal insights and improve predictions of pest outbreaks (*1*, *2*).

The value of long-term data. Recent studies of data sets spanning over 1000 years have shed light on the environmental factors that influence the population cycles of larch budmoths (**left**) and Chinese migratory locusts (**right**).

Caterpillars of the larch budmoth (see the figure, left) can reach densities of 30,000 per tree when they defoliate larch trees and inhibit tree growth, effects detectable as narrow growth rings. Esper *et al.* recently examined larch wood from the European Alps dating back 1173 years (*1*). The results show that budmoth outbreaks have occurred every 9.3 years on average since 844 C.E.; the authors attribute their absence since 1981 to contemporary warming, which stimulates early egg development and premature hatching. This may be good news for the trees, but is it yet another sign of the effects of anthropogenic climate change?

Thinking of insects' activities more than a thousand years ago recalls biblical accounts of plagues of desert locusts, but there is no continuous historical record of such plagues before the 20th century. However, a Chinese Emperor instigated the sporadic collection of data on Chinese migratory locusts (see the figure, right) as early as 707 B.C.E., and his successors maintained a continuous series of annual records from 957 C.E. (*3*–*5*). Stige *et al.* have now reanalyzed these data in the context of rainfall and temperature changes (*2*). As in time series of desert locusts (*6*), brown locusts (*7*), and Australian plague locusts (*8*), the data are not insect numbers but proxies based on numbers of administrative areas infested. Significant relationships with rainfall can be found in all of these locusts, but how rainfall affects the insects' survival may vary according to species, depending on whether they have eggs that can remain dormant for a year or longer and so survive droughts, and on the spatiotemporal distribution of the rain. For the Chinese locusts, Stige *et al.* show that both floods and droughts are important, with temperature and rainfall interacting to set the scene (*2*). The study also emphasizes the importance of low-frequency phenomena, which involve effects discernible at time scales longer than a year. These are known in many ecosystems and were detected in desert and brown locusts as unexplained 16- and 17-year cycles, respectively (*6*, *7*).

Previous studies of the Chinese locust (*3*–*5*) focused on interannual rather than longer-term variations, with one notable exception showing that population variability increased at longer time-scales (*9*). Stige *et al.* have now re-examined the data at lower frequencies than annual. In a kind of ecological archaeology, they used mean decadal temperature (derived from ice cores, tree ring data, lake sediments, and contemporary records) and mean decadal rainfall (based on samples of juniper that tally with precipitation indices) to show that there were more locusts when the climate was cold and wet and fewer when it was warm and dry.

The authors find that these climatic effects accounted for locust variability for periodicities of 30 years or more. Decadal frequencies of droughts and floods have a multiplicative effect on the locusts. Both droughts and floods are more common in cold, wet periods, conditions associated with high locust numbers because droughts allow the insects to lay eggs on riverbanks and lakesides; retreating floods also provide ideal breeding conditions. These responses detected at decadal scales have important practical implications: A projected warming Chinese climate would be expected to lead to fewer locusts as a result of a reduced breeding habitat, despite a positive association between locusts and temperature at the annual scale (*3*).

Frequency-dependent effects of this kind may need to be taken into account to correctly interpret other phenomena liable to disruption by global warming, such as wind systems

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that affect locust migrations and the mixing of swarms originating from different sources. Examinations at finer scales than the whole of China and further understanding of the interactions between subpopulations are needed. Desert locusts, for instance, have regional populations whose dynamics are cross-correlated (*10*).

Further insights from China are likely after the compilation of meteorological and ecological records from the past 3000 years (*11*). Science needs such long data sets and the financial commitments to provide them. Some series could be reconstructed, as in the larch budmoth case, but finding biological data sets on a par with those for the budmoths and locusts will need imagination and help from historians. The Chinese Emperors thought long term, and so should we, by maintaining current data collection programs essential for the understanding of contemporary phenomena in the short, medium, and very long term, perhaps 1000 years hence.

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MICROBIOLOGY

Deadly Priming

Roberto Kolter

Bacteria behave like cells of a multicellular organism, secreting a molecule that primes a subpopulation to commit suicide during stressful conditions.

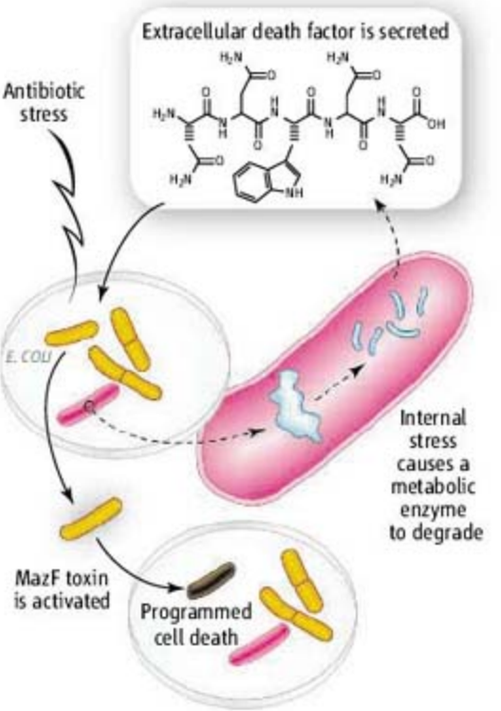
Constituent cells of an organism communicate with each other through chemical signals to coordinate growth and differentiation. Cells also perish along the way, their programmed death benefiting the organism's survival (*1*). Bacteria also "talk" to each other through chemical signals and, on occasion, kill themselves (*2*, *3*). This suggests that they are capable of multicellular behaviors (*4*). On page 652 of this issue, Kolodkin-Gal *et al.* show that the bacterium *Escherichia coli* releases a signaling molecule that activates a programmed cell death pathway, supporting the concept that multicellularity is a general bacterial trait (*5*).

Programmed cell death mechanisms in bacteria often follow a common theme: A lethal toxin is constitutively produced and, at the same time, an antitoxin is made for protection (*3*). When synthesis of both is maintained, the bacterial cell survives even though the antitoxin is usually more labile than the toxin. But when their synthesis is arrested, the greater lability of the antitoxin eventually unmasks the toxin's activity, leading to the cell's demise. The lethal effect of these toxins can be due to a variety of activities, such as inhibiting DNA replication or translation.

Bacterial toxin-antitoxin systems were first found encoded in plasmids, autonomously replicating extrachromosomal elements whose inheritance is not always guaranteed upon cell division. However, any cell that fails to inherit the plasmid will soon find itself without any antitoxin and dead. The surprise came when similar toxin-antitoxin coding modules were found in bacterial chromosomes. Why would a bacterium want to kill itself? Such a response makes little sense for an individual cell. But when that cell is a member of a multicellular aggregate, its death could benefit the rest. For example, the development of fingers in a human embryo requires the cells between the fingers to undergo programmed cell death.

Many of the known stimuli that trigger programmed cell death in bacteria are environmental stresses, such as exposure to antibiotics or ultraviolet light. Kolodkin-Gal *et al.* now demonstrate that for these stresses to be effective, a self-generated signal must also be present. Prior results indicated that toxin-mediated cell death could only be observed in cultures with high population density (*6*). Kolodkin-Gal *et al.* determined that cell-free medium from a high-density culture can induce programmed cell death in cultures with low population density. The culprit turned out to be a linear pentapeptide in the medium.

Perhaps the most exciting finding in this report is the source of the pentapeptide. Many self-generated, secreted signaling molecules in bacteria are small molecules, including peptides (*2*). So the fact that the "extracellular death factor" discovered by Kolodkin-Gal *et al.* is a peptide should come as no surprise. But the peptide signals described in earlier studies are encoded in small genes that generate prepeptides, which are processed to yield the signaling molecule. What is striking about the *E. coli* peptide is that it is derived from the degradation of glucose-6-phosphate dehydrogenase, a metabolic enzyme (see the figure). Although the exact pathway leading to the production of this pentapeptide remains to be defined, it seems reasonable that it is made when the bacterium, for reasons unknown, begins to destroy this enzyme. Thus, an apparent internal stress, such as the onset of starvation, could generate this signal, which is secreted (perhaps by some moribund cells in the population) and primes the population such that some cells can be killed through the pro-



Spreading the message. A bacterial metabolic enzyme is degraded, yielding a peptide that is released. When sensed by cells in conjunction with environmental stresses, such as antibiotic exposure, toxin-mediated programmed cell death is triggered.

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grammed cell death pathway when confronted with other stresses.

How does this "extracellular death factor" function? Does it feed into the toxin-antitoxin programmed cell death pathway directly, or does cell death result from synergistic interaction between multiple cellular pathways? The finding raises the possibility that there are analogous molecules—degradation products from normal cell components—that serve as signals to communicate specific physiological changes in subpopulations of cells to the entire community. This certainly adds a whole new dimension to how and why bacterial cells talk to each other.

Kolodkin-Gal *et al.* use "quorum sensing" to frame their findings, a term first used to describe the function of many secreted bacterial signaling molecules to a broad audience (*7*). Cells produce signaling molecules at a constant rate such that the concentration of these molecules within a given volume is proportional to the number of cells. By sensing the molecule, cells in the populations are said to "count their numbers." The results of Kolodkin-Gal *et al.* demonstrate, however, that the term as applied to any self-generated signal may be somewhat limiting. The Argentine philosopher Ernesto Sábato said that any attempt to explain relativity by talking of trains moving at a station does not explain relativity (*8*). Perhaps explaining bacterial behaviors by analogy to the numbers of members required to be present at a meeting shortchanges the intricacies of bacterial physiology. Sensing a molecule generated from the demise of a metabolic enzyme is perhaps telling the bacterium more than just how many cells are present. Quorum sensing has been a wonderful addition to the language of microbiology, but we must realize that bacteria can clearly tell each other much more than just their numbers.

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ASTRONOMY

Pulsars 40 Years On

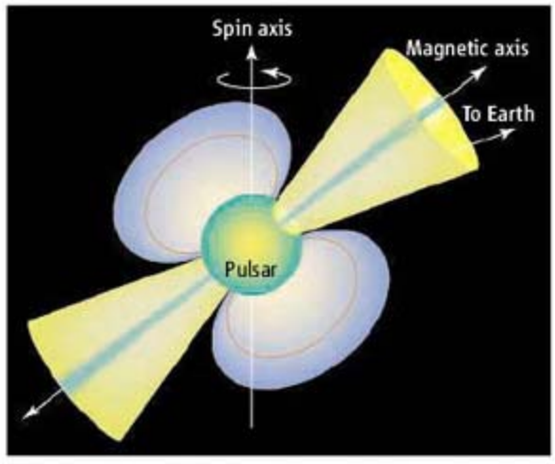
The discovery of pulsing radio signals from spinning stars in 1967 is still influencing astrophysics today.

Jocelyn Bell Burnell

Discovering a new object in the universe is a lot like downhill skiing. Standing outside the summit hut looking around, we feel our feet slither a little and we begin sliding. We go with the glide and then realize we're on a new track, bidding farewell to the hut and its comforts. There are other skiers with us, whooping and shouting as the pace picks up. Recognizable features whoosh by. There are forks and diversions, some left unexplored. Sometimes the trees fall back, opening wide vistas to be explored, and we take different tracks across those patches. It's a long hill, the slope is still steep, and the valley floor continues to fall away before us. So it was with the discovery and subsequent study of the spinning neutron stars called pulsars (*1*).

Other researchers will recall experiencing the adrenaline rush as a new field opens up in front of them. Although the skiing analogy captures my sense of the excitement and thrill of the development of a new field of astrophysics, it may not fairly represent the decades of hard work by many colleagues, which at times must have felt uphill.

It has been 40 years since neutron stars, in the guise of pulsating radio stars (pulsars), were discovered (*2*). My colleagues and I at Cambridge University had built a radio telescope by stringing hundreds of kilometers of wire over a thousand wooden poles. Our goal was to detect quasars (quasistellar sources) that had been recognized as the most distant detectable objects in the universe and also extremely powerful sources of radio waves. Several months into the data collection, I noticed a series of regular radio pulses in the midst of a lot of receiver noise. After initial anxieties that there was radio interference or a fault with the equipment, it became clear that we were dealing with neutron stars, which are small in radius but large in mass (and therefore also large in density). The significance of the discovery dawned gradually and, indeed, is still developing.



Cosmic lighthouse. Pulsars are spinning neutron stars that emit radio beams from their tilted north and south magnetic poles. The radio beams sweep across the sky, appearing on Earth as highly regular radio pulses.

The high density of neutron star interiors, comparable to the density of the nucleus of the atom (imagine the world's population crammed into a sewing thimble) has led to some interesting condensed matter physics. We now understand the physics of the outer layers of a neutron star, yet we still do not know what is in the center—quarks, kaons, pions, Bose-Einstein condensates—any of them are possible. And the higher mass neutron stars now being found probably require such exotic components.

We now understand that a pulsar behaves like a cosmic lighthouse (see the figure), swinging a radio beam around the sky as it rotates. As the beam sweeps across Earth, radio telescopes pick up a pulse. Pulsars are less than 20 km across and typically rotate several times a second. The fastest, however, goes at 700 revolutions per second—staggering when you realize they have a mass of 10^{27} metric tons. However, once a body of this mass is rotating, it takes a lot to change its rotation, so the pulse period is accurately maintained. The pulsar is an excellent clock.

The existence of such clocks opened up the field of experimental relativity (*3*). Using pulsars, researchers have discovered gravitational radiation, as predicted by Einstein. Precision timing also shows when a pulsar is in a binary star system, orbiting a compan-

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ion star. We now know of many pulsars in such binary systems, including several where both stars are neutron stars and one system where both are pulsars. Exquisite precision measurements allow detection of the precession of the orbit, the inward spiraling of the two stars, the gravitational redshift, and other phenomena predicted by the theory of general relativity, and confirm that theory to the 0.05% level.

Although we understand the precision of pulsars, we still do not understand the mechanism that produces the radio emission. And while it seems sensible that the rotation should gradually slow (typically the period has increased by 1 second since the extinction of the dinosaurs), we do not really understand the slowing-down mechanism either. Furthermore, some pulsars have "glitches"—the pulsar rotation speeding up suddenly—and a full explanation of that is still pending. Precision timing of a pulsar allows the detection of the wobble produced by planets orbiting it, and we know of two (or maybe three) pulsars with planets. Two or three is a difficult number to explain given that we know of around 2000 pulsars. You would expect none, but if we accept that our understanding is incomplete and that there must be a way of keeping or creating planets around pulsars, then surely there should be many more.

Astronomers working in the high-energy x-ray and gamma-ray wavebands have added to the interest by finding objects that look just like pulsars but are mostly "radio quiet." Pulsar magnetic fields are believed to be large (a million million times Earth's magnetic field), but some of the x-ray and gamma-ray pulsars, known as magnetars, have fields that are a thousand times larger still.

And so it has gone on, amazing result followed by jaw-dropping discovery. Although the field is 40 years old, it is showing no sign of settling down into middle age—quite the opposite. At the moment, we seem to be in a phase where we are discovering "peculiar pulsars." Unusual (or, more fairly, unexpected) types of pulsar or neutron star are coming to light, and we suspect we've seriously underestimated the number of neutron stars in the Galaxy. Now we have intermittent pulsars, which are quiet more than they pulse but still accurately maintain the pulse phase (*4*, *5*). We also have to revise our understanding of the supernovae explosions that create neutron stars.

Forty years is approximately a scientist's working lifetime, and those who joined this new field as graduate students or postdocs are now reaching retirement age. However, the community is young and vigorous, with excellent leadership, so will continue to thrive. The large radio telescopes that the community uses were almost all in existence when pulsars were discovered, although the receivers and the computing facilities used with those large telescopes have improved immensely. But if that much can be done with 50-year old telescopes, what will the new generation of telescopes like the Square Kilometer Array (*6*) and its precursors reveal?

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EVOLUTION

The Sharp End of Altruism

Simulations show that war drives the joint evolution of altruism and hostility to outsiders.

Holly Arrow

Which would you prefer: a society of selfish but tolerant freetraders, or a warrior society in which people help one another but are hostile to outsiders? If you value both altruism and tolerance, neither seems ideal. Societies of tolerant altruists, however, are exceedingly rare in the simulation presented by Choi and Bowles on page 636 of this issue (*1*). Instead, altruism flourishes only in the company of outgroup hostility (parochialism), with war as both the engine of this coevolutionary process and its legacy. For a compatriot, the parochial altruist who risks his life is a shining knight, whereas the outsider encounters the sharp end of this altruism.

CREDIT: PETER HOEY

From an evolutionary perspective, altruism—acts that benefit others at a personal cost—is puzzling. Some influential theories that address this puzzle are kin altruism (*2*), the tendency to help blood relations; and reciprocal altruism (*3*), the tendency to help people who are likely to return the favor. Neither explains generosity to non-kin when costs are high and reciprocation unlikely. Heroism in warfare is an example. Explaining such extravagant altruism via indirect benefits to altruists and their kin has proved difficult. A growing body of work seeks instead to explain altruism with models that include selection on both individuals and groups.

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In such "multilevel" models (*4*), the evolutionary outcome depends on the relative impact of competing pushes and pulls at individual and group levels. Individual selection pushes counterproductive behaviors like altruism out of the gene pool. Group selection exerts a contrary pull, favoring groups with many altruists over groups of more selfish folk. In most species, individual selection wins out. For humans living in small groups, however, a strong group selection pull is plausible. Evidence that intergroup violence killed a nontrivial proportion of our ancestors (*5*) has fueled interest in war as a force for robust group selection. War is a strong candidate because people kill each other based on group membership.

In Choi and Bowles' simulation, 20 small groups of agents interact over thousands of generations. Agents have two genes, each with two alleles. They are either tolerant (T) or parochial (P) and either altruistic (A) or not (N). Offspring inherit their parents' traits, with occasional random mutations. Altruists help fellow group members at a personal cost; non-

altruists do not. Tolerant agents have lucrative exchanges with outsiders; parochial agents do not. A high proportion of parochials in groups restricts trading opportunities for all.

Among the four possible combinations of traits, TN is the most profitable. These self-interested traders profit both from contact with outsiders and from the donations made by altruists. The most costly combination is PA. These generous warriors make donations and also risk their lives to protect noncombatants and conquer new territory for the group's offspring. Individual selection favors the T and N alleles over the P and A alleles. Victory in war favors groups with more PA types over those with fewer. The other two trait combinations are PN bullies, who are both hostile and selfish, and TA philanthropists, who both trade and donate to others.

In each generation, groups are randomly paired. What happens next depends on the proportions of tolerant types and warriors in the paired groups. If two highly tolerant groups are paired, tolerant members reap the benefits of trade. If the proportion of tolerant types drops below a strong majority in either group, however, the likelihood of peaceful trade plummets. Instead, the groups have either an unproductive standoff or a war. If both groups have the same numbers of warriors, a standoff results. War becomes increasingly likely the greater the imbalance of power, and wars end in a victory or a draw. Some proportion of warriors are killed regardless of outcome. In a victory, however, many civilians on the losing side are also killed, and offspring from a postwar baby boom among the victors migrate into the conquered territory.

The societies that evolve are stable in two conditions: when either selfish traders (TN) or generous warriors (PA) are the dominant type. A few PN bullies and even fewer TA philanthropists can coexist within trader or warrior regimes. The trading regime is peaceful. Standoffs and wars are more common in the warrior regime, but even infrequent war—10 to 20% of encounters—can maintain high levels of parochial altruism. Similar findings for the impact of intermittent war on the evolution of heroism (*6*) suggest that war need not be "constant" to act as a powerful selective force.

The convergence of altruism and parochialism in Choi and Bowles' simulation is consistent with links between the two found in behavioral studies. Selfish choices in social dilemma experiments, for example, diminish markedly when the game is embedded in an intergroup context (*7*). The boost in altruism caused by awareness of an outgroup is also more marked among women than men (*8*), consistent with war exerting stronger selective pressure on males as warriors. Interestingly, altruism levels for women, although relatively unaffected by intergroup hostility, were still high. It appears that the relative importance of alternative evolutionary pathways to altruism may differ for men and women.

A full accounting of such pathways must include cultural evolution. In other work, Bowles and colleagues show how norms can support altruism by promoting conformity (*9*). In the current simulation, warrior-rich groups enforce a trading ban. However, this norm is predetermined. An obvious extension would be to allow norms to evolve. Can pro-trade norms outcompete more isolationist parochial norms? Do norms that punish cowards naturally coevolve with war and altruism?

The simulation findings suggest that one legacy of war is an inherent tension between tolerance and altruism. Cross-cultural studies, however, provide grounds for optimism. In one study, people from 15 small-scale societies played a donation game (*10*). Average generosity correlated with the amount of market exchange and economic cooperation typical in the society. By adding mutable norms to the simulation, the potential viability of societies of tolerant altruists could be further explored.

A better understanding of how our impulses to give, to trade, and to attack outsiders are intertwined should help in the quest to promote pro-social behavior while keeping the sharp end of altruism sheathed.

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ATMOSPHERE

Call Off the Quest

Myles R. Allen and David J. Frame

Knowledge of the long-term response of Earth's climate to a doubling of atmospheric carbon doixide may be less useful for policy-makers than commonly assumed.

Over the past 30 years, the climate research community has made valiant efforts to answer the "climate sensitivity" question: What is the long-term equilibrium warming response to a doubling of atmospheric carbon dioxide? Earlier this year, the Intergovernmental Panel on Climate Change (*1*) concluded that this sensitivity is likely to be in the range of 2° to 4.5°C, with a 1-in-3 chance that it is outside that range. The lower bound of 2°C is slightly higher than the 1.6°C proposed in the 1970s (*2*); progress on the upper bound has been minimal.

On page 629 of this issue, Roe and Baker (*3*) explain why. The fundamental problem is that the properties of the climate system that we can observe now do not distinguish between a climate sensitivity, S, of 4°C and $S > 6$°C. In a sense, this should be obvious: Once the world has warmed by 4°C, conditions will be so different from anything we can observe today (and still more different from the last ice age) that it is inherently hard to say when the warming will stop. Roe and Baker formalize the problem by showing how a symmetric constraint on the strength of the feedback parameter f (which determines how much energy is radiated to space per degree of surface warming) gives a strongly asymmetric constraint on S. The reason is simple: As f approaches 1, S approaches infinity. Roe and Baker illustrate the point with the information provided by recent analyses of observed climate change, atmospheric feedbacks, and "perturbed physics" experiments in which uncertain parameters are varied in climate models.

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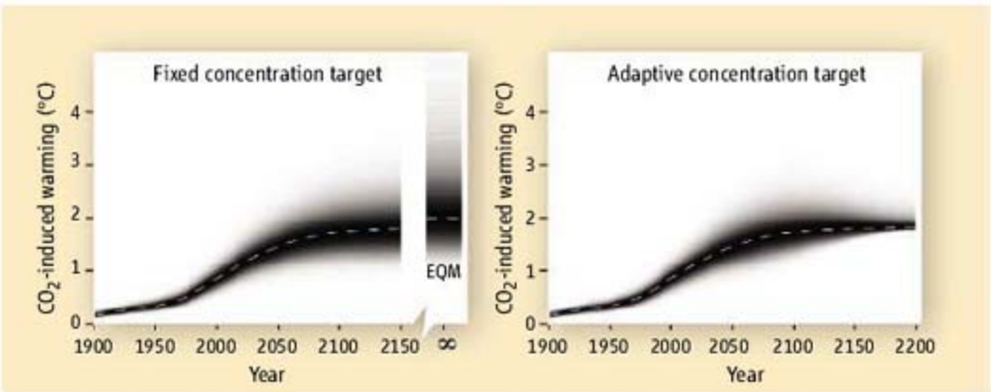
It might be objected that some models that displayed high sensitivities in perturbed physics experiments also poorly reproduce the energy budget at the top of the atmosphere (*4*) and hence perform poorly in short-term climate forecasts (*5*). Likewise, the fact that direct studies of atmospheric feedbacks provide only a weak constraint on S does not mean that no stronger constraint is possible. But these objections miss Roe and Baker's main point: The fact that uncertainties in climate processes add up to give an approximately Gaussian uncertainty in f means that there are innumerable ways of generating a climate model with f close to unity and hence a very high S. Ruling all of these out requires us to find observable quantities that are consistently related to S in all physically plausible climate models, and to show that observations of these quantities are inconsistent with a high S. Despite much searching, such observations remain elusive.



Carbon dioxide–induced warming under two scenarios simulated by an ensemble of simple climate models. (Left) CO_2 levels are stabilized in 2100 at 450 ppm; **(right)** the stabilization target is recomputed in 2050. Shading denotes the likelihood of a particular simulation based on goodness-of-fit to observations of recent surface and subsurface-ocean temperature trends (*7*, *8*). Simulations are plotted in order of increasing likelihood, so worse-fitting models are obscured. The bar labeled "EQM" shows the models' likelihood against their long-term equilibrium warming at 450 ppm. How these likelihoods are translated into forecast probabilities is controversial, and the more asymmetric the likelihood function, the greater the scope for controversy.

There are even more fundamental problems. Roe and Baker equate observational uncertainty in f with the probability distribution for f. This means that they implicitly assume all values of f to be equally likely before they begin. If, instead, they initially assumed all values of S to be equally likely, they would obtain an even higher upper bound. This sensitivity of the results to prior assumptions shows that the real problem with the upper bound on climate sensitivity is not that it is high (in which case we could hope that more data will bring it down), but that it is controversial: Opaque decisions about statistical methods, which no data can ever resolve, have a substantial impact on headline results.

All this would be very bad news if avoiding dangerous anthropogenic interference in the climate system required us to specify today a stabilization concentration of carbon dioxide (or equivalent) for which the risk of dangerous warming is acceptably low. Fortunately, we do not need to.

To understand why, consider two scenarios for carbon dioxide–induced warming, based on large numbers of runs of a simple climate model constrained by recent temperature observations (*6*–*10*). In the first scenario, carbon dioxide concentrations are stabilized at 450 ppm from 2100 onward. If S turns out to be close to our current best estimate, then achieving this concentration target gives an eventual equilibrium warming of 2°C (see the figure, left, dashed line). But S is uncertain; thus, even if we stabilize at 450 ppm, we cannot rule out much more than 2°C of eventual warming, as shown by the shaded plume. Notice that observed temperature trends provide a much stronger constraint on forecast warming even 50 years after stabilization than on the long-term equilibrium response (shown by the bar labeled EQM). Hence, if the true climate sensitivity really is as high as 5°C, the only way our descendants will find that out is if they stubbornly hold greenhouse gas concentrations constant for centuries at our target stabilization level.

In reality, of course, our descendants will revise their targets in light of the climate changes they actually observe. Suppose that, in 2050, they simply divide our 450-ppm target forcing by the fraction by which the observed carbon dioxide–induced warming trend between 2000 and 2050 over- or underestimates our current best-guess forecast (*11*). They then recompute concentration paths to stabilize at this revised level in 2200.

The long-term carbon dioxide concentration consistent with a 2°C warming (which we call C2K) is currently uncertain, but the risk of a low (and hence expensive) C2K is much better constrained by data than is the risk of a high (and hence dangerous) climate sensitivity. This is because C2K, like f, scales approximately with things we can observe, and hence is not subject to the problems that bedevil efforts to constrain sensitivity. The uncertainties in how the available policy levers translate into global emissions, and how emissions translate into concentrations through the carbon cycle, are so large that uncertainty in the final concentration we are aiming for in 2200 is probably the least of our worries—provided we resist the temptation to fix a concentration target early on. Once fixed, it may be politically impossible to reduce it.

The temperature response to this adaptive-stabilization scenario (see the figure, right) is much better constrained because it depends on current trends, not on S. If S turns out to be toward the upper end of the current uncertainty range, we may never find out what it is: Some models with $S = 4$°C are effectively indistinguishable from others with $S = 6$°C under this scenario. But provided our descendants have the sense to adapt their policies to the emerging climate change signal, they probably won't care.

An upper bound on the climate sensitivity has become the holy grail of climate research. As Roe and Baker point out, it is inherently hard to find. It promises lasting fame and happiness to the finder, but it may not exist and turns out not to be very useful if you do find it. Time to call off the quest.

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10.1126/science.1149988

EPPENDORF 2007 WINNER

Neural Circuits Underlying Chemical Perception

The olfactory circuit in fruit flies is mapped out by combining genetic tools with in vivo measurements of neural activity.

Rachel I. Wilson

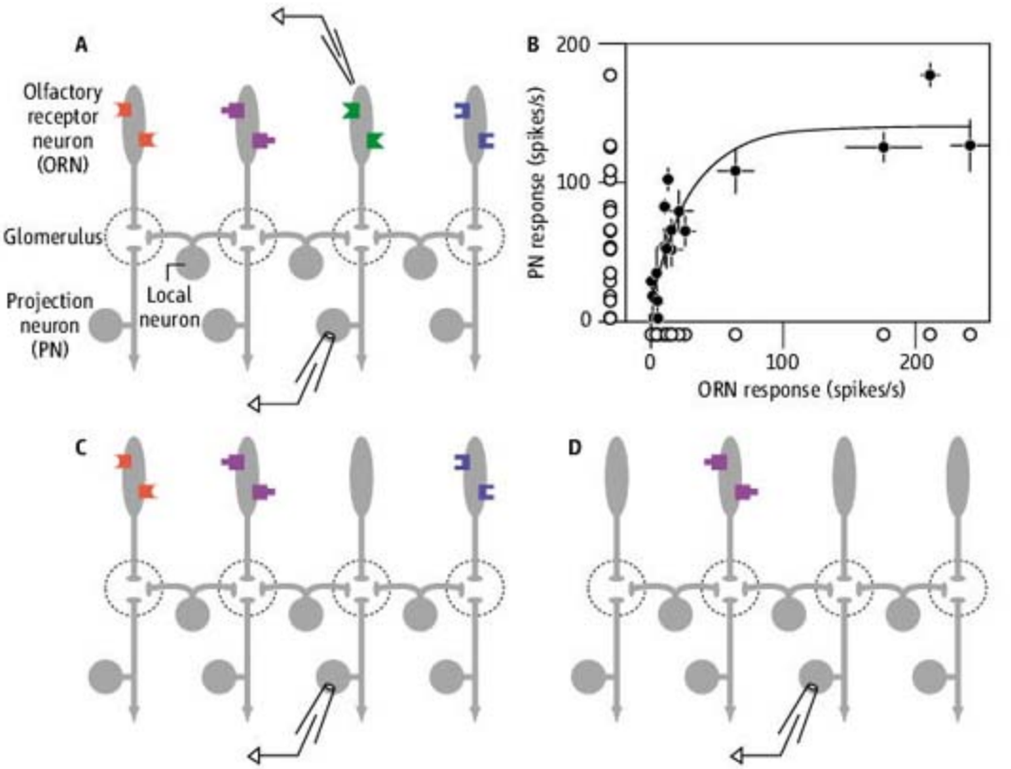
Eppendorf and *Science* are pleased to present the prize-winning essay by Rachel Wilson, the 2007 winner of the Eppendorf and *Science* prize for Neurobiology.

The air around us is full of chemical signals—plumes of smelly molecules floating in the breeze. Most animals are constantly alert to these olfactory cues. Odors can signal the quality of a food source, the location of a danger zone, or the sexual status of a potential mate. Initially, these signals are transduced by receptor neurons in the nose (or in insects, by receptor neurons in the antennae). Olfactory information is then passed to the brain via a series of electrical impulses in the axons of these neurons. Importantly, individual types of olfactory receptor neurons (ORNs) are not dedicated to sensing a particular odor. Instead, each ORN type can respond to multiple different odors (*1*). This confers an enormous coding capacity on the olfactory system. Thus, in order to identify an odor, the brain must decode a distributed pattern of impulses from a diverse population of receptor inputs.

My lab's goal is to understand how the brain solves this problem. Our mission is simplified by the beautiful organization of the olfactory system: All the ORNs expressing the same odorant receptor gene project their axons to the same compartment (termed a glomerulus) in the brain (*2*). Each second-order neuron in the brain receives direct input from just a single ORN type. Individual glomeruli thus represent discrete processing channels (see the figure, panel A). Glomeruli are also interconnected by local neurons, although the function of these lateral connections is not well understood. Recently, we performed a series of experiments asking what computations occur within an individual processing channel and how lateral connections contribute to these computations.

These questions are technically difficult to address in the vertebrate olfactory bulb. Therefore, we turned to the fruit fly *Drosophila melanogaster*. The fly antennal lobe shares the basic organization of the olfactory bulb, but is comparatively simpler, with only ~50 glomeruli as compared to ~1000 in mice (*3*, *4*). We can genetically label neurons that are either pre- or postsynaptic to specific glomeruli, allowing us to monitor activity in identified cells. In collaboration with colleagues at the California Institute of Technology, I recently developed techniques for making electrophysiological recordings from single neurons in the adult *Drosophila* brain in vivo (*5*). This allows us to exploit the sensitivity of electrophysiological recording techniques in a simple and genetically tractable invertebrate nervous system.

First, we asked what computations occur as information moves through the antennal lobe. We recorded odor responses in vivo from both ORNs and second-order neurons (termed projection neurons, or PNs; see the figure, panel A) corresponding to seven different glomeruli. We found that, for each glomerulus, the odor responses of PNs differ from the responses of their presynaptic ORNs. Whereas ORNs are somewhat narrowly tuned to odors, PNs are more broadly tuned. This distributes odor representations more efficiently within a PN's dynamic range (see the figure, panel B). We also found that, on average, the signal-to-noise



Decoding olfactory signals. (**A**) Recording from ORNs and their cognate PNs. Unlike the situation in this simplified cartoon, each glomerulus contains the axons of ~40 ORNs and the dendrites of about four PNs. (**B**) PN responses differ from the responses of their presynaptic ORNs. Plot shows the responses of ORNs and PNs corresponding to the same identified glomerulus (glomerulus DM1). Each black circle represents the response to a different odor, averaged across experiments (±SEM). Projecting the data onto each axis (white circles) illustrates that odor responses are distributed more uniformly in PN coding space than in ORN coding space. [Panel reproduced from (*6*)] (**C**) Silencing one type of ORN in order to observe lateral inputs onto its postsynaptic PNs. (**D**) Confining ORN input to one glomerulus in order to map its lateral inputs onto other glomeruli.

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ratio of a PN's odor responses is better than that of an ORN's responses. Finally, we showed that these two transformations together can increase the separability of odor representations (*6*).

In these experiments, we focused on neurons responsive to "typical" odors (fruity odors, plant volatiles, and other odors representative of major chemical classes). Next, we asked whether odors with special behavioral relevance are processed in the same way as the "typical" odors. Other investigators had previously reported that one type of neuron in the antennae responds to cis-vaccenyl acetate, a *Drosophila* pheromone (*7*, *8*). We found that these ORNs are very narrowly tuned, responding to this pheromone but not to any other odors in our test set. In behavioral experiments, we found that genetically ablating these ORNs abolishes innate attraction to the pheromone. When we recorded from PNs postsynaptic to the glomerulus targeted by these ORNs, we found that, like their direct presynaptic inputs, these PNs are very narrowly tuned to cis-vaccenyl acetate. Thus, these PNs are unusual: They are exclusively dedicated to one ligand. This special circuit may ensure a tight connection between a pheromonal stimulus and a hardwired behavioral response (*9*).

Finally, returning to "typical" glomeruli, we asked how lateral connections shape PN odor responses. Here we exploited the fact that mutation of an odorant receptor gene silences all the ORNs that normally express that receptor. We reasoned that, by recording from a PN postsynaptic to silent ORNs, we could directly observe the effect of odor-evoked lateral inputs onto that PN (see the figure, panel C). Surprisingly, we found that lateral synaptic connections onto PNs are mainly excitatory. Control experiments showed that these connections exist in normal flies, not just mutants. We then genetically engineered flies where only one type of ORN is functional, and recorded from PNs postsynaptic to silent ORNs (see the figure, panel D) in order to map the pattern of connections from the functional receptors onto other glomeruli. This experiment showed that lateral excitatory connections are spatially widespread, heterogeneous in strength, and obey connectivity rules that are stereotyped across flies (*10*). At about the same time, another group independently discovered a new class of cholinergic local neurons in the fly antennal lobe (*11*), suggesting a possible cellular substrate for the excitatory connections we had found. These lateral excitatory connections may contribute to broad PN tuning. Alternatively, they may serve to bring all PNs transiently closer to their spike threshold whenever one receptor type is activated, thereby increasing their sensitivity.

Taken together, our results show that a major transformation of olfactory signals occurs in the antennal lobe, and that integration across different glomerular channels begins here, in the first relay of the olfactory system. More broadly, these studies demonstrate the feasibility of deconstructing a simple neural circuit using genetic tools combined with in vivo measurements of neural activity. Decades ago, experiments in an invertebrate model organism (the squid) yielded key insights into how nerve cells produce electrical impulses; these experiments in *Drosophila* illustrate how invertebrates are helping neuroscientists bridge the conceptual gap between cells and circuits to understand the logic of neural computations.

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10.1126/science.1151362

2007 Grand Prize Winner

The author of the prize-winning essay, **Rachel Wilson**, received her AB degree in chemistry from Harvard in 1996. She began her training as a neurophysiologist with Helmut Haas at Heinrich-Heine-Universität in Düsseldorf and continued as a graduate student with Roger Nicoll at the University of California, San Francisco. In her graduate work, she showed that endogenous cannabinoids act as retrograde messengers at hippocampal synapses. In 2001, she joined Gilles Laurent's laboratory at the California Institute of Technology as a postdoctoral fellow. There, in collaboration with another postdoctoral fellow, Glenn Turner, she developed methods for performing whole-cell recordings from neurons in the adult *Drosophila* brain in vivo. In 2004, she joined the Department of Neurobiology at Harvard Medical School. Her laboratory uses small neural circuits to study fundamental principles of sensory processing.

Finalist

Marianne Hafting Fyhn, for her essay, "The Grid Map in the Brain." Dr. Fyhn was born in Morehead City, North Carolina, USA, and grew up in Bergen, Norway. She did her undergraduate studies in biology at the Universities of Bergen, Oslo, and Tromsø before completing her master's thesis at the University of Tromsø in 1999 with work in Arctic biology at Spitsbergen. In 2000 she started her graduate work in neurobiology at the Centre for the Biology of Memory under the supervision of Dr. May-Britt and Dr. Edvard Moser at The Norwegian University for Science and Technology, Trondheim. She performed in vivo recordings of spatially modulated neurons from the hippocampus and entorhinal cortex of freely behaving rats and discovered "grid cells," which are neurons in entorhinal cortex with a remarkable hexagonal activity pattern. Since receiving her Ph.D. in 2005, she has been a postdoctoral fellow at the Centre for the Biology of Memory. Dr. Fyhn is a hiking, mountaineering, and fishing enthusiast. She has two small children with whom she enjoys outdoor activities.

CREDIT: (RIGHT) TORKEL HAFTING

For the full text of Dr. Fyhn's essay and for information about applying for next year's awards, see *Science* Online at www.sciencemag.org/feature/data/prizes/eppendorf/eppenprize.shtml.

INTERNATIONAL

AAAS Strikes Landmark Agreements to Build Long-Term China Engagement

BEIJING—With China emerging as a world research power, top AAAS officials and their Chinese counterparts signed a series of cooperative agreements that could serve as the foundation for future collaborations on a range of critical science and technology issues.

The 6-day trip to Beijing, Shanghai, and Hangzhou also included a conference, organized by the China Association for Science and Technology (CAST) and AAAS, that brought together dozens of scholars and researchers from both nations to discuss scientific integrity and social responsibility. The meeting provided an opportunity to discuss efforts by both countries to address challenges that trouble the entire global research enterprise, as well as some possible areas of future collaboration such as ethics education and joint studies on specific cases.

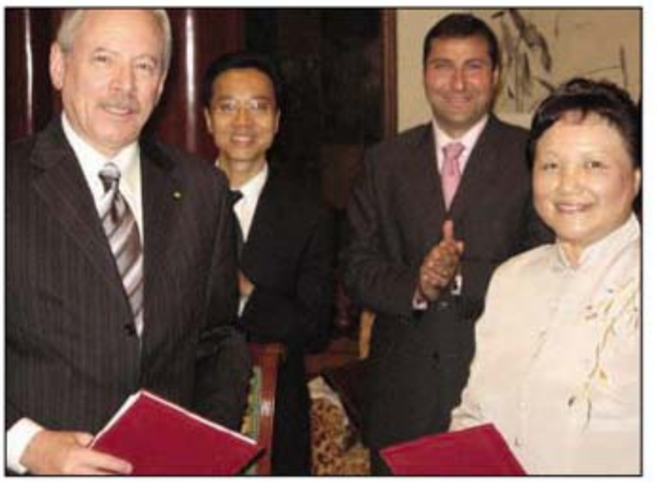
The AAAS delegation, led by Chief Executive Officer Alan I. Leshner, held substantive talks with some of China's most senior S&T leaders, including Minister of Science and Technology Wan Gang; Deng Nan, chief executive secretary of CAST; Lu Yongxiang, president of the Chinese Academy of Sciences (CAS); Shen Wenqing, who serves both as vice president of the National Natural Science Foundation of China and chairman of the Shanghai Association for Science and Technology; and Yang Wei, President of Zhejiang University.

Wan Gang, Minister of Science and Technology

Under one agreement, Project 2061, AAAS's pioneering science literacy initiative, will provide materials that can be translated and posted on the CAST Web site. Leshner and Lu signed a separate memorandum of understanding to select, translate, and distribute 33 high-impact papers from the past decade of the journal *Science*.

Leshner and Deng also signed an overarching agreement to seek collaborative projects on a range of possible issues, including sustainability; public understanding of science and engineering; science education; and creating S&T opportunities for women.

"I believe that CAST and AAAS have common issues…and we're serving similar functions in our countries," Deng said in talks before a signing ceremony. "I believe that allows us to have even more cooperation in the broader fields of science."



From left to right: Alan I. Leshner, chief executive officer of AAAS and executive publisher of *Science*; Sun Mengxin, deputy director-general for international affairs at the China Association for Science and Technology (CAST); Vaughan Turekian, AAAS chief international officer; and Deng Nan, chief executive secretary of CAST

"Our organizations are similar and unique in their size and breadth of activities," replied Leshner, who also serves as executive publisher of *Science*. "Our collaboration has advantages not only for our countries, but also for the whole world….It's very important that we take every opportunity to collaborate on our common interests."

The new agreements and the ethics conference—resulting from months of trans-Pacific discussions—are landmarks in an ambitious new engagement between AAAS and the Chinese S&T community. The journal *Science*, published by AAAS, opened its first Chinese news office in Beijing this month, to be staffed by veteran correspondent Richard Stone. EurekAlert!, AAAS's science news service, this month debuted a new Chinese-language portal to serve the nation's journalists, researchers, businesses, and government.

Leshner described the China trip, from 24 to 29 September, as "highly informative and extremely constructive." The AAAS delegation also included Vaughan Turekian, AAAS chief international officer, and Tom Wang, AAAS director for international cooperation. Mark S. Frankel, director of AAAS's Scientific Freedom, Responsibility and Law Program, played a lead role in organizing the conference and in Beijing meetings with the Chinese Medical Association and the CAS Institute of Zoology.

"We are in an era of unprecedented global cooperation in science and technology—cooperation that not only advances the underlying sciences, but also addresses some of the major global challenges that we all face," Turekian said. "The collaboration between Chinese and U.S. scientists, and in fact all members of the global science enterprise, will lead to more creative science and technological developments that will improve people's lives."

The new engagement comes at a time of remarkable growth and emergence for China. Beginning some 2000 years ago, it achieved monumental breakthroughs in astronomy, medicine, mathematics, and technology. Today, following 30 years of reform and opening to the West, its economy is soaring. Shanghai and Beijing have become major world centers for business, culture, and tourism; next year, the nation will host the Summer Olympics.

Before he moved into government, Chinese President Hu Jintao was a hydraulic engineer; today, the government's "Scientific Development Perspective" is a framework for addressing China's complex economic, environmental, and international challenges.

To address climate change, the government in June announced plans to restructure the economy, promote clean energy technologies, and improve energy efficiency. China launched its first manned space mission in 2003; it is expected to send its first spacecraft to orbit the moon before year's end. In July, the China Internet Network Information Center reported that 162 million Chinese were connected to the Web; while that remains just a fraction of the nation's 1.3 billion people, in the first half of this year, an average of 100 new residents per minute logged on for the first time.

According to CAST, China's total investment in research and development nearly tripled between 2000 through 2005. A 2006 report by the U.S. National Science Foundation (NSF)

called the R&D spending increases "unprecedented for any country in recent memory."

In the bilateral talks and at the 2-day AAAS/CAST conference—"China-U.S. Workshop on Scientists' Social and Ethical Responsibilities"—Chinese science officials discussed lessons learned and new approaches they are taking to address some of the challenges created by the dynamic growth of their scientific enterprise. Participants on both sides shared their experiences dealing with ethical lapses and other more serious misconduct resulting from this high-stakes environment.

(l-r) Chen Sai-juan, vice chair of CAST; Laurel Baldwin-Ragaven, Henry R. Luce Professor of Health and Human Rights at Trinity College; and Shen Wenqing, vice president of National Natural Science Foundation of China.

During their meeting, Leshner and Wan Gang, China's S&T minister, discussed their views on the role of increased science competition in developing strong science in both countries, as well as the pressures to succeed confronting students and researchers at every level.

Qian Yi, a professor and environmental scientist at Tsinghua University, described several cases in which advanced students were caught in violations—falsifying a C.V., falsely claiming authorship of a paper, theft of research data. In one case, she said, an accomplished young scholar committed an infraction because he was competing for a major academic prize. "He was trying to make himself perfect," she said.

Shen Wenqing, vice president of the National Natural Science Foundation of China, said his organization created an ethics panel in 1998. From that year through 2004, he said, the committee received an average of 92 complaints a year and averaged about nine enforcement actions. In 2006, he said, 150 complaints generated 50 disciplinary actions.

Scholars and science policy experts in the U.S. delegation found the problems remarkably similar to those at home. The conference demonstrated that integrity "has been recognized as a key national issue by the highest level of the Chinese science communities," said William Y. Chang, director of the NSF Beijing office.

Karen Holbrook, the former president of Ohio State University, added that she was struck "by how very similar we are in our beliefs about the need for science and scientists to demonstrate complete integrity in their work—that it is a responsibility and implicit in the privilege of conducting scientific investigation."

Chinese S&T leaders and members of the AAAS delegation said the budding relationship should lead to collaboration on a variety of issues, including scholar exchange programs; science museums and public engagement; and sustainability.

Creating opportunities for continuing engagement made the China trip "tremendously important" for both countries, Leshner said. "I believe it sends a very important signal to the rest of the global scientific community about our shared seriousness about these critical issues."

EDUCATION

Black Colleges Event Explores Road to Success

African-American undergraduate students often find a nurturing environment at historically black colleges and universities but must make connections outside of these schools if they want to be successful researchers, education experts advised a gathering of the young scientists this month.

Prominent researchers gathered at the National Science Foundation Historically Black Colleges and Universities Undergraduate Program (HBCU-UP) conference, held 4 to 7 October and organized by AAAS, urged their soon-to-be-colleagues to get outside the classroom as much as possible to experience the rigors of a real-life science career.

"It is very important that young scientists connect into the larger scientific community by publishing, networking and getting internships," said Camille McKayle, National Science Foundation Program Director for HBCU-UP. "[Research] is not about staying within your own comfort zone, but rather stepping outside."

Students attending the meeting, one of the nation's largest for African-American undergraduate scientists, had many opportunities to step out of that comfort zone, including sessions where they were grilled on their research methods and participated in networking exercises among more than 700 students and faculty in attendance.

Speakers also praised the job that HBCUs are doing to produce a new generation of minority researchers. In a written statement to the group, Rep. Eddie Bernice Johnson (D-TX) said HBCUs provide a learning environment that allows students of color to learn skills and gain confidence to achieve in any environment. In 2000, HBCUs graduated 40% or more of all African Americans who received degrees in physics, chemistry, astronomy, environmental sciences, mathematics, and biology, according to Johnson.

The conference was arranged by AAAS with a 3-year, $975,000 NSF grant, but the organizers hope to find additional co-sponsors for the 2008 meeting. "We had a long waiting list for exhibitors and heard over and over from professors that they wanted to bring more students but just did not have the travel money," said Yolanda George, deputy director of Education and Human Resources at AAAS. "Those are great signs, and we hope to harness that enthusiasm next year."

—Benjamin Somers and Molly McElroy

2007 ELECTION

AAAS Council Reminder

The next meeting of the AAAS Council will take place during the AAAS Annual Meeting and will begin at 9:00 a.m. on 17 February 2008 in Boston, Massachusetts, in the Republic Ballroom of the Sheraton Boston Hotel.

Individuals or organizations wishing to present proposals or resolutions for possible consideration by the Council should submit them in written form to the AAAS Chief Executive Officer Alan Leshner by 19 November 2007. This will allow time for them to be considered by the Committee on Council Affairs at their fall meeting. Items should be consistent with AAAS's objectives and be appropriate for consideration by the Council. Resolutions should be in the traditional format, beginning with "Whereas" statements and ending with "Therefore be it resolved."

Late proposals or resolutions delivered to the AAAS Chief Executive Officer in advance of the February 2008 Open Hearing of the Committee on Council Affairs will be considered provided that they deal with urgent matters and are accompanied by a written explanation of why they were not submitted by the November deadline. The Committee on Council Affairs will hold its open hearing at 2:30 p.m. on 16 February 2008 in the Commonwealth Room of the Sheraton Boston.

Summaries of the Council meeting agenda will be available during the annual meeting at both the AAAS Information Desk and in the AAAS Headquarters office. A copy of the full agenda will also be available for inspection in the Headquarters Office in the Hynes Convention Center.

AAAS Members Elected as Fellows

In October, the AAAS Council elected 471 members as Fellows of AAAS. These individuals will be recognized for their contributions to science and technology at the Fellows Forum to be held on 16 February 2008 during the AAAS Annual Meeting in Boston. The new Fellows will receive a certificate and a blue and gold rosette as a symbol of their distinguished accomplishments. Presented by section affiliation, they are:

Section on Agriculture, Food, and Renewable Resources

Lajpat R. Ahuja, U.S. Department of Agriculture • J. Ole Becker, University of California, Riverside • Henry Daniell, University of Central Florida • Mark B. David, University of Illinois at Urbana-Champaign • Peter J. Hansen, University of Florida • Andrew Hiatt, Mapp Biopharmaceutical, Inc. • Zhanjiang Liu, Auburn University • Steven A. Lommel, North Carolina State University • Joyce Loper, U.S. Department of Agriculture • John M. Norman, University of Wisconsin-Madison • Jeffrey F. Pedersen, U.S. Department of Agriculture • Robert E. Sharp, University of Missouri-Columbia • David R. Shaw, GeoResources Institute • Richard Stouthamer, University of California, Riverside • Jeremy F. Taylor, University of Missouri-Columbia • Barbara Valent, Kansas State University • Robert Zeigler, International Rice Research Institute

Section on Anthropology

Alan H. Bittles, Edith Cowan University • Peter T. Ellison, Harvard University • Yohannes Haile-Selassie, Cleveland Museum of Natural History • Richard F. Kay, Duke University • Timothy Kohler, Washington State University • Carl A. Maida, University of California, Los Angeles • Sally McBrearty, University of Connecticut • Stephen T. McGarvey, Brown University Medical School • Dennis H. O'Rourke, University of Utah • Peter J. Richerson, University of California, Davis • Robert V. Riordan, Wright State University • Lawrence M. Schell, University at Albany, State University of New York • Sara Stinson, City University of New York, Queens College • Linda D. Wolfe, East Carolina University

Section on Astronomy

Paul D. Feldman, The Johns Hopkins University • John T. Gosling, University of Colorado • Ronald Greeley, Arizona State University • Carle M. Pieters, Brown University • S. Alan Stern, Southwest Research Institute • John H. Thomas, University of Rochester • Joel E. Tohline, Louisiana State University

Section on Atmospheric and Hydrospheric Sciences

Donald R. Blake, University of California, Irvine • Judith A. Curry, Georgia Institute of Technology • Russell R. Dickerson, University of Maryland • Seyed M. Hassanizadeh, Utrecht University • Philip K. Hopke, Clarkson University • Conway B. Leovy, University of Washington • Dennis P. Lettenmaier, University of Washington • W. Timothy Liu, Jet Propulsion Laboratory • Paul A. Mayewski, University of Maine • Donald J. Wuebbles, University of Illinois at Urbana-Champaign

Section on Biological Sciences

Farid E. Ahmed, East Carolina University • John F. Alderete, University of Texas Health Science Center • J. David Archibald, San Diego State University • Steven E. Artandi, Stanford University School of Medicine • Karen Artzt, University of Texas at Austin • Laura D. Attardi, Stanford University • Aimée H. Bakken, University of Washington • Bonnie Bartel, Rice University • Mark A. Batzer, Louisiana State University • Philip W. Becraft, Iowa State University • Marlene Belfort, University at Albany, State University of New York • Judith Berman, University of Minnesota • Stephen M. Beverley, Washington University School of Medicine • Debashish Bhattacharya, University of Iowa • Pamela J. Bjorkman, California Institute of Technology • Jef D. Boeke, The Johns Hopkins University School of Medicine • Kathleen Boris-Lawrie, Ohio State University • Toby Bradshaw Jr., University of Washington • Steven P. Briggs, University of California, San Diego • Morris J. Birnbaum, University of Pennsylvania • Douglas G. Capone, University of Southern California • Martin Chalfie, Columbia University • Perng-Kuang Chang, U.S. Department of Agriculture • Robert W. Chapman, South Carolina Department of Natural Resources • Ambrose L. Cheung, Dartmouth Medical School • Sarah F. Covert, University of Georgia • Elizabeth A. Craig, University of Wisconsin-Madison • Larry B. Crowder, Duke University Marine Laboratory • Michael R. Culbertson, University of Wisconsin-Madison • Jim E. Cutler, Children's Hospital of New Orleans • Salil K. Das, Meharry Medical College • R. Kelly Dawe, University of Georgia • Titia de Lange, Rockefeller University • Raymond J. Deshaies, California Institute of Technology • Ann E. Desjardins, U.S. Department of Agriculture • Claude Desplan, New York University • John F. X. Diffley, Cancer Research UK • Machi F. Dilworth, National Science Foundation • Walter H. Doerfler, University of Cologne • William L. Duax, Hauptman-Woodward Medical Research Institute • Anindya Dutta, University of Virginia School of Medicine • William C. Earnshaw, University of Edinburgh • Walter Eckhart, Salk Institute • Howard J. Edenberg, Indiana University School of Medicine • David R. Engelke, University of Michigan • Ellen H. Fanning, Vanderbilt University • Robert L. Fischer, University of California, Berkeley • Errol C. Friedberg, University of Texas Southwestern Medical School • Elaine Fuchs, Rockefeller University • Philip Furmanski, Rutgers University • George M. Garrity, Michigan State University • Sankar Ghosh, Yale University School of Medicine • Stephen P. Goff, Columbia University • Yale E. Goldman, University of Pennsylvania • J. Eric Gouaux Jr., Oregon Health & Sciences University • Barbara J. Graves, University of Utah • Nig D.F. Grindley, Yale University • Mary Lou Guerinot, Dartmouth College • Thomas J. Guilfoyle, University of Missouri-Columbia • James F. 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INTRODUCTION

Decisions, Decisions . . .

WHO HASN'T AGONIZED OVER A MAJOR DECISION IN LIFE, WHETHER TO accept a job offer, move house, or perhaps switch research fields? We are confronted with a multitude of decisions on a daily basis. Many decisions are trivial and can be dealt with in seconds. However, others may have wider ramifications and can be excruciatingly complicated. In the past few years, our understanding of the underlying processes of decision-making has progressed markedly. This neuroscience special issue highlights some of the most exciting developments in this area.

Koechlin and Hyafil (p. 594) review recent experimental studies that provide new insights into the function and connectivity of the anterior prefrontal cortex, which forms the apex of the executive system underlying decision-making. The authors propose an original model of the anterior prefrontal function and provide a theoretical framework for addressing major unresolved issues and guiding future research on decision-making and higher cognition.

Human beings are highly social animals. Many of our decisions make sense only within a social environment. Sanfey (p. 598) outlines the advantages that can be gained by combining tasks and formal mathematical models from game theory with modern neuroimaging methods to characterize the processes that underlie social decision-making. He also summarizes recent research that offers good examples of how this neuroeconomic approach has already begun to illuminate our knowledge of this process.

Sometimes things can also go wrong in this complicated and well-balanced interplay between several brain regions. Paulus (p. 602) proposes that decision-making in psychiatric populations cannot be viewed simply as an alteration of the preference structure or the way individuals experience the outcome of the decision. Instead, it must be understood from the homeostatic balance perspective of the individual. Increased risk-taking behavior in drug addicts, for example, although maladaptive in the generic sense, may actually be adaptive for the substance user in a complex, highly unpredictable environment while attempting to respond to internal urges and cravings.

Decision theory has boomed in the past decade. Körding (p. 606) gives an overview of how decision theory, including normative/Bayesian approaches, can lead us to better understand the functions of the nervous system.

At *Science*'s Signal Transduction Knowledge Environment (http://stke.sciencemag.org), the emphasis is on the "decisions" made by cells. A Perspective by Coskun *et al.* concerns the role of the tyrosine phosphatase SHP2 in the decision of a progenitor to become a neuron or a glial cell. Another by Nichols discusses the role of ATP-sensitive potassium channels in linking metabolism with excitability, highlighting the effects of a ketogenic diet on the decision of a neuron to fire.

You will now have to decide whether to turn the page and read all the contributions in detail, quickly flick through the section, or skip it altogether.

– PETER STERN

Decision-Making

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Science

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REVIEW

Anterior Prefrontal Function and the Limits of Human Decision-Making

Etienne Koechlin* and Alexandre Hyafil

The frontopolar cortex (FPC), the most anterior part of the frontal lobes, forms the apex of the executive system underlying decision-making. Here, we review empirical evidence showing that the FPC function enables contingent interposition of two concurrent behavioral plans or mental tasks according to respective reward expectations, overcoming the serial constraint that bears upon the control of task execution in the prefrontal cortex. This function is mechanistically explained by interactions between FPC and neighboring prefrontal regions. However, its capacity appears highly limited, which suggests that the FPC is efficient for protecting the execution of long-term mental plans from immediate environmental demands and for generating new, possibly more rewarding, behavioral or cognitive sequences, rather than for complex decision-making and reasoning.

Decision-making is the realm of the frontal lobes, ranging from the simplest choice, for example, choosing an apple or a pear from a fruit basket, to the most complex ones like deciding the next move in a game of chess. Decision-making is subserved by a hierarchy of lateral frontal cortex regions controlling action selection in relation to internal drives and subjective preferences, the apex of which corresponds to the lateral convexity of the cyto-architectonic area defined as Brodmann's area 10, the so-called frontopolar cortex (FPC) (Fig. 1A) (*1*). The FPC is tremendously well developed in humans compared with other primates (*2*), and brain imaging has provided evidence that it contributes to uniquely human traits like reasoning or problem-solving. However, the FPC is not a homuncular command center responsible for orchestrating cognition in lower brain regions. Patients with FPC lesions show no significant impairments on formal neuropsychological tests of perception, language, and intelligence but appear markedly impaired in decision-making in open-ended and ill-structured situations, which often occur in everyday life (*3*). These observations suggest that the FPC has evolved as a functional "add-on," perhaps to overcome the limitations of more posterior prefrontal processes by enabling the emergence of more flexible cognitive control in the service of decision-making.

The characterization of FPC function is a major issue in current cognitive neurosciences, not least because it has the potential to reveal an upper bound to human executive function. Here, we review recent brain imaging studies that provide important new insights into FPC function. The FPC enables contingent interposition of multiple mental tasks or behavioral plans, the function that allows humans to overcome the serial constraint upon control processes evident in more posterior prefrontal regions (*4*). We describe a simple neurocomputational model delineating the basic computational properties of this FPC function and explaining its mechanistic implementation in neuronal interactions between FPC and neighboring prefrontal regions.

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FPC Contributions to Human Cognition

Learning and exploration. The FPC is robustly engaged when subjects are instructed to learn new behavioral routines (*5*–*7*). This engagement is observed in both reinforcement (*5*, *7*) and supervised (*6*) learning paradigms, indicating that the FPC contributes to explicit learning regardless of the type of learning or feedback. However, in contrast to more posterior prefrontal regions, the FPC gradually disengages over the course of learning (*6*). This disengagement occurs as subjects switch back and forth between alternative behavioral options (exploration), drawing upon feedback to progressively eliminate irrelevant choices. Indeed, to a greater extent than other prefrontal regions, FPC activity specifically correlates with the amount of uncertainty (i.e., entropy) remaining between multiple putative options that subjects are simultaneously tracking (*8*) (Fig. 1C). Moreover, FPC is active whenever subjects depart from an a priori optimal option to check alternative ones (*9*). Thus, the FPC contribution to learning and exploration appears to be associated with maintaining and switching back and forth between multiple behavioral alternatives in search of optimal behavior.

Memory retrieval. The FPC is also engaged in episodic memory tasks, in which subjects are instructed to judge whether multiple serially presented stimuli have been previously encountered in specified past episodes (*10*). The FPC is generally involved in such episodic retrieval paradigms regardless of the nature of past episodes and stimuli, retrieval success, or stimulus novelty (*11*). The FPC is tonically active during retrieval (*12*), in preparation for subsequent retrieval (*13*) and also in response to probe stimuli that occur less frequently (*14*). The involvement of the FPC thus cannot be accounted for by memory retrieval per se but is likely to be accounted for by the task structure requiring scheduled retrieval of multiple elements of a past episode. This view has recently received direct experimental support: FPC activity in episodic retrieval tasks is virtually identical to that underlying categorization tasks that require a combination of multiple cognitive subtasks (*15*, *16*). Thus, FPC activations observed in episodic retrieval paradigms are likely to result from the coordination of subtasks involved in those paradigms, including the recurrent retrieval of multiple elements of past episodes and the demands of the judgment task pertaining to each stimulus.

Relational reasoning. The FPC is involved in relational reasoning, in which subjects are required to integrate the outcomes of multiple inferences for selecting appropriate responses. This has been observed for various types of inferences, including perceptual (*17*, *18*) and semantic (*19*) inferences. More generally, the FPC is engaged whenever subjects must integrate the outcomes of multiple internal subtasks, for example, when deciding whether multiple items share the same property (*15*, *16*) or, conversely, whether a single item jointly exhibits multiple properties (*20*). Is the FPC active only at the final integration stage, when multiple outcomes are combined to reach a decision (*10*), or does the FPC underlie the passing of information between successive computational stages in the service of eventual integration? Recent experimental results rule out the former hypothesis (*21*), because FPC activity was observed even in the absence of a final integration stage, and the FPC exhibited sustained activations in the intermediate phase preceding final integration. Instead, in relational reasoning, the FPC allows the buffering of information from previously executed subtasks while subsequent stages are being carried out.

Multitasking behaviors. Finally, the FPC is robustly engaged in multitasking behaviors, in which subjects postpone the execution of one task to perform another first (*22*). Multitasking recruits the most anterior regions in the FPC (*23*) (Fig. 1B) and is selectively and severely altered in patients with FPC lesions (*24*). Moreover, unlike other prefrontal regions, the FPC involvement in multitasking is not reducible to component processes such as task-switching or task-delaying (*22*). The FPC specifically exhibits sustained activations associated with postponed tasks that resist distraction and ongoing performance regardless of the nature of tasks (*25*, *26*). Task contingency underlying multitask-

ing behaviors is also a key factor in activating the FPC, given that it is not engaged during the execution of structured superordinate plans composed of multiple embedded tasks (*27*). Overall, these findings indicate that the FPC specifically subserves the ability to contingently switch back and forth between independent tasks by maintaining distractor-resistant representations of postponed tasks during the performance of another.

The Core Function of the FPC

The lateral prefrontal regions are involved in selecting and maintaining action selection rules (i.e., task sets) according to the immediate context and/or the ongoing temporal episode in which the person is acting (*28*). This lateral prefrontal system obeys a serial principle, which allows only a single task set to govern action selection at any one time (*4*). Such a serial constraint minimizes conflict situations that may arise between multiple task sets and thus optimizes action selection. The FPC overcomes this serial constraint by enabling the joint consideration of multiple task sets in a wide variety of behavioral paradigms. Collectively, the data depicts an anterior prefrontal system in which lateral prefrontal regions select and maintain the task set governing ongoing action, whereas the FPC enables previously selected task sets to be maintained in a pending state for subsequent automatic retrieval and execution upon completion of the ongoing one. This process, which we call "cognitive branching," forms a domain-general core function at the basis of the behaviors and mental activities requiring simultaneous engagement in multiple tasks that are not serially organized into a single, pre-established superordinate plan (*27*).

Accordingly, the branching process enables a task or a behavioral episode to be temporarily suspended while another is being performed, or conversely allows reversion to a pending task or episode following completion of the ongoing one, even in the absence of any external cues. Such an ability is especially impaired in patients with frontopolar lesions (*24*). Moreover, the branching process is critical for relational reasoning, because the maintenance of pending task sets associated with previously computed inferences during subsequent inferential tasks (and reverting back to such pending representations) is required for integration. For example, in the calculation $(2 + 4) \times (5 + 7)$, the first addition is computed (= 6), then the operand/task-set 6 is maintained in a pending state while the second addition is computed (= 12). Then, reverting back to the pending operand will cue the multiplicative operation 6×12, leading to the final result (= 72) (*21*). The branching process is also critical for exploration and tree-search because it allows switching in and out of "branches" or behavioral options while maintaining others that are pending (*9*) (*8*). Although episodic memory retrieval presumably does not require branching processes, it is likely that cognitive branching is engaged in a series of multiple, concurrent retrieval trials. The branching process may be involved in performing the judgment task pertaining to each trial while maintaining specified past episodes in a pending state so as to internally retrieve them subsequently for preparing the next memory judgment trial. Also, episodic or "source" memory may require subjects to hold data in a pending state and switch between the putative episodes with which the retrieval probe could have been associated. Finally, compared with more posterior prefrontal processes, the key feature of branching processes is to enable resumption of pending task sets in the absence of any external cues or associations between the ongoing and pending task sets, so that the execution of pending task sets is only triggered by termination of the ongoing task. Consequently, when contingency, uncertainty, or entropy over task sets decreases—for example, when serial associative links develop among several task sets because of training or simply when the number of possible task sets shrinks—the need for branching processes decreases and the FPC is expected to disengage. In agreement with this hypothesis, the FPC disengages when contingency, uncertainty, or entropy over multiple task sets decrease during learning (*6*), exploration (*8*), or multitasking (*27*) (Fig. 1C). Thus, the branching hypothesis accounts for the FPC involvement in a wide variety of behavioral paradigms, which suggests that cognitive branching forms core function of the FPC. This function substantiates the more phenomenological view that the FPC plays a pivotal role in switching between externally versus internally oriented thoughts (*3*) (supporting online text).

A Neurocomputational Model of FPC Function

It remains to be described how the anterior prefrontal system "decides" to place an ongoing task into a pending state and to revert back to it later. This is a key theoretical issue, given that the FPC is not under the control of higher brain centers. The FPC is specifically engaged when subjects suspend the execution of an ongoing task set associated with a priori the largest expected future rewards in order to explore a possibly more rewarding task set (*9*). The result suggests that with no supervisory optimization, cognitive branching occurs between two concurrent behavioral options, when reward expectations associated with each option (or expected penalties if not executed) are large enough so that it would be too costly or risky to simply abandon one. In that event, comparing the rewards expected from executing each option

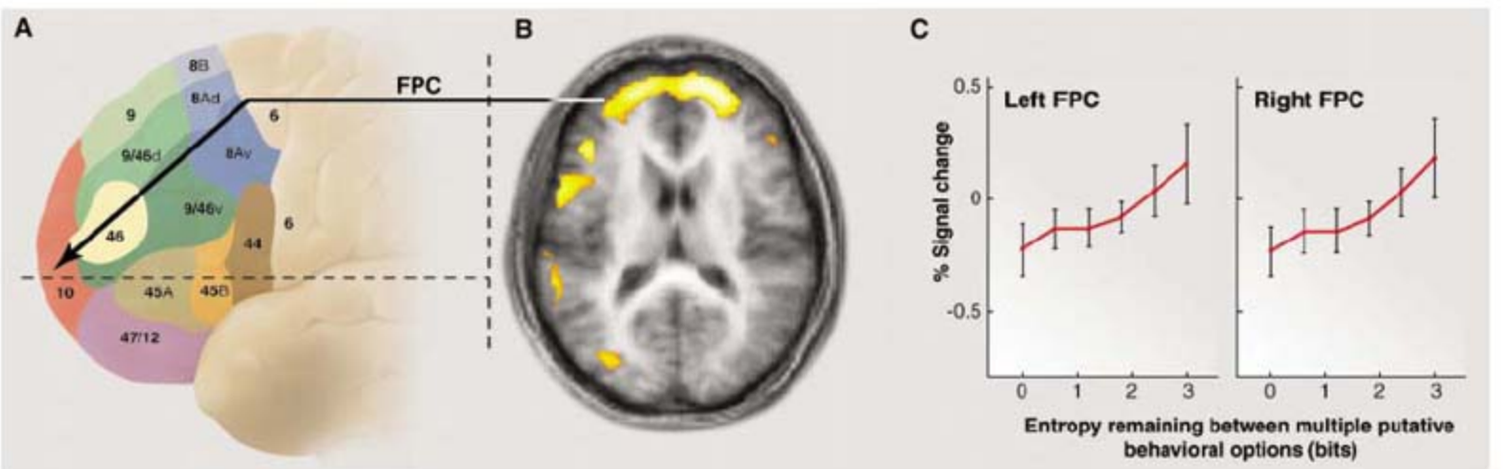

Fig. 1. The human frontopolar cortex. (**A**) The FPC corresponds to the lateral Brodman's area 10 (red region), the most rostral portion of the human prefrontal cortex [from (*35*)]. (**B**) FPC activation observed with functional magnetic resonance imaging (fMRI) on a horizontal brain slice (dashed line indicates approximate localization) in multitasking behavior, in which subjects postponed the execution of a task to perform another first [from (*27*)]. (**C**) fMRI also revealed that FPC activity correlated with the amount of uncertainty (i.e., entropy) remaining between multiple putative behavioral options that subjects were simultaneously tracking while exploring a virtual maze [from (*8*)].

immediately will determine which option is placed in a pending state (the less rewarding one) and which one is selected for guiding immediate behavior (the more rewarding one). We proposed a minimal neurocomputational model showing how the FPC (denoted *Fpc*) may mechanistically implement reward-based cognitive branching with no supervisory optimization through interactions with neighboring prefrontal regions, namely, the anterior lateral and medial/orbital prefrontal regions (denoted *Lpc* and *Ofc*, respectively) (*29*) (Fig. 2 and supporting online text). In accordance with empirical results (*28*, *30*, *31*), the model assumes that *Lpc* neurons represent the active task set guiding current behavior, that is, active *Lpc* units through top-down projections select and maintain task-set specifications represented in other brain regions and required for execution (typically caudal prefrontal regions), whereas *Ofc* neurons code for the future rewards expected from executing task sets. *Lpc* and *Ofc* neurons are reciprocally connected and receive input signals from other brain regions (typically posterior associative and paralimbic cortices) cueing activity toward specific task sets and updating expected future rewards. By contrast, *Fpc* neurons are reciprocally connected to *Lpc* and *Ofc* neurons only, with an inhibitory influence of *Lpc* onto *Fpc* neurons. Overall, according to reward expectations, *Fpc* units form a possible back-up buffer for storing a previously selected task set in *Lpc*, while *Lpc* units are representing another. Subsequently, the *Fpc* buffer enables to possibly reinstantiate in *Lpc* the pending task set and consequently to reinstantiate its specifications in lower brain regions for execution, even in the absence of any external inputs.

Computer simulations show that this neuronal system forces *Lpc* and *Fpc* neurons to potentially select and maintain only the two most rewarding task sets. The other task sets are discarded. Cognitive branching occurs between the two most rewarding task sets, provided that the second largest expected reward is larger than a given threshold *Rb* (Fig. 3 and fig. S1). The most and second-most rewarding task sets are then selected and encoded in *Lpc* and *Fpc* neurons as the active and pending task set, respectively (Fig. 3, C and D). Consistent with experimental data (*25*), *Lpc* and *Fpc* neurons show sustained activation during the pending period. This situation perpetuates (or possibly reverses according to updated relative reward values) until one expected reward value drops below threshold *Rb* (e.g., because of task completion). If this value corresponds to the active task set, *Lpc* neurons start encoding the pending task set and *Fpc* activity returns to background noise level: the active task set is discarded and the pending task set becomes the active one for guiding subsequent behavior, thereby achieving a branching between the two task sets (Fig. 3C). Conversely, if the value corresponds to the pending task set, this one is discarded from the *Fpc* and branching is aborted (Fig. 3D). Also, no branching occurs if the second-largest expected reward does not reach the reward threshold *Rb* (Fig. 3, A and B). In that event, no sustained activity occurs in *Fpc* neurons during the execution of the most rewarding task set. The second-most rewarding task set is discarded, and the system does not revert back to it in the absence of any subsequent external cueing. However, consistent with experimental data (*32*), *Fpc* neurons may exhibit short phasic responses to external cues associated with multiple task sets (Fig. 3D).

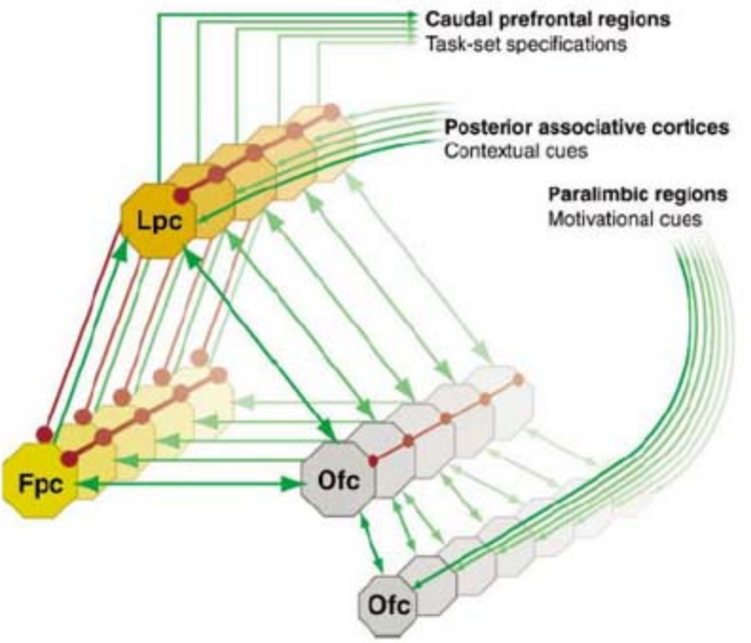

Fig. 2. A neurocomputational model of the frontopolar function. Octagons represent neuronal populations in the lateral prefrontal (*Lpc*), medial/orbital frontal (*Ofc*), and frontopolar (*Fpc*) cortex. Green and red arrows indicate excitatory and inhibitory interactions, respectively. Strong lateral inhibition within *Lpc* and *Fpc* enforces task-set selection; strong self-excitation (not shown) enables task-set maintenance in the absence of any external inputs. By contrast, weak lateral inhibition and self-excitation within *Ofc* enables *Ofc* neurons to maintain reward expectations related to multiple task sets, but only those corresponding to the task sets maintained in *Lpc* and *Fpc*. All interactions between *Ofc*, *Lpc*, and *Fpc* neurons are excitatory except the influence exerted by *Lpc* on *Fpc* neurons, which is assumed to be inhibitory. The inhibitory influence of *Lpc* onto *Fpc* neurons forces *Lpc* and *Fpc* to encode distinct task sets. *Ofc* also includes an input layer storing and updating expected reward values associated with task sets with respect to input signals (e.g., external or internal contextual cues, feedback, and task end-states). Neuron activity is governed by standard activation dynamics equations (supporting online text).

In sum, the second most rewarding task is placed in a pending state in the FPC, while lateral prefrontal regions are controlling the execution of the most rewarding task, provided that the future rewards expected from the two task sets are large enough (>*Rb*). Thus, cognitive branching occurs and FPC is recruited with no supervisory optimization and control, because it would have been too costly to discard the second most rewarding task as suggested by empirical results (*9*). The model indicates that the reward threshold *Rb* for branching and recruiting FPC is larger than the minimal expected reward (*Ra*) required for triggering task execution and recruiting lateral prefrontal regions (Fig. 3 and fig. S1). The model also shows that reward expectations associated with the active and pending task sets are continuously updated with respect to feedback signals related to current behavior. In particular, if reward expectations associated with the pending task set drop below the reward threshold *Rb* for branching, cognitive branching is aborted and the pending task set is discarded. This predicts that the anterior prefrontal system enables online evaluation of the pending task set according to the outcomes of a distinct, ongoing task, an ability referred to as the valuation of fictive action that may considerably speed up learning and exploration (*33*).

This model does not aim to describe in detail neural coding of task sets in the anterior prefrontal regions. Nevertheless, it explains how the processing of cognitive branching may mechanistically emerge from neuronal interactions between FPC and neighboring prefrontal regions. The model provides a predictive theoretical framework within which we can empirically address several unresolved major issues about the FPC function and its relationships with other prefrontal functions, including the processing of internal drives and subjective preferences in the medial and orbital sectors of the prefrontal cortex (*30*, *31*).

In particular, a key prediction is that the capacity of the FPC cannot exceed the processing of a single pending task at any one time: According to the model, the anterior prefrontal system can process only the two most rewarding task sets, even if they are associated with identical expected reward values. Interferences

supervene in *Fpc*, when three or more distinct task sets are associated with the two largest expected reward values, in which case cognitive branching is dramatically impaired (supporting online text, fig. S2). Thus, the model especially predicts that the FPC is unable to recursively perform cognitive branching—resuming a primary and secondary pending task after completion of a third task—because interferences supervene between the two pending tasks. This prediction has been recently tested in our laboratory in a behavioral protocol that recruits the FPC and requires subjects to engage in multitasking behaviors. Our data confirm the prediction. We observed that compared with various control conditions, postponement of a second task to execute a third task while a first was already pending led to marked selective impairment in subsequently resuming the first and second pending tasks. Thus, the model and these preliminary results support the idea that the prefrontal executive system lacks the computational power to perform recursive cognitive branching, and consequently to control recursive tree-searches in the exploration of deep branching sets of future possible situations underlying reasoning, problem-solving, or complex decision-making.

This predicted, rather limited capacity of the FPC may appear surprising, given that humans can indeed carry out such complex decision-making. However, a complex decision situation may become tractable as expertise with a particular situation is acquired, reducing uncertainty and contingency during exploration. One possible hypothesis is that extensive training leads to the formation of mental spatial maps of branching sets, so that with expertise, recursive tree-searches reduce to spatial navigation, which relies on specialized brain structures like the parietal cortex and hippocampus. Alternatively, the property of recursion is a key feature of human language (*34*), and it is conceivable that expertise may lead to the formation of specific language-like coding systems mapping particular tree-structures and allowing to track complex and recursive exploration. Thus, the FPC capacity limit described above implies that complex decision-making in well-established situations does not critically rely on FPC. Consistently, frontopolar patients show few decision-making deficits in well-established situations such as standardized tests of intelligence, although they are impaired in open-ended and ill-structured situations (*3*).

Concluding Remarks

On the basis of recent empirical findings and neurocomputational mechanisms, we suggest that the processing of cognitive branching based on reward expectations with no supervisory optimization forms the core function of the anterior prefrontal cortex. This function partially overcomes the serial constraint that bears upon the control of mental tasks in the lateral prefrontal cortex, providing an additional degree of flexibility to the prefrontal executive system, which may be critical for the emergence of human higher cognitive abilities such as reasoning and

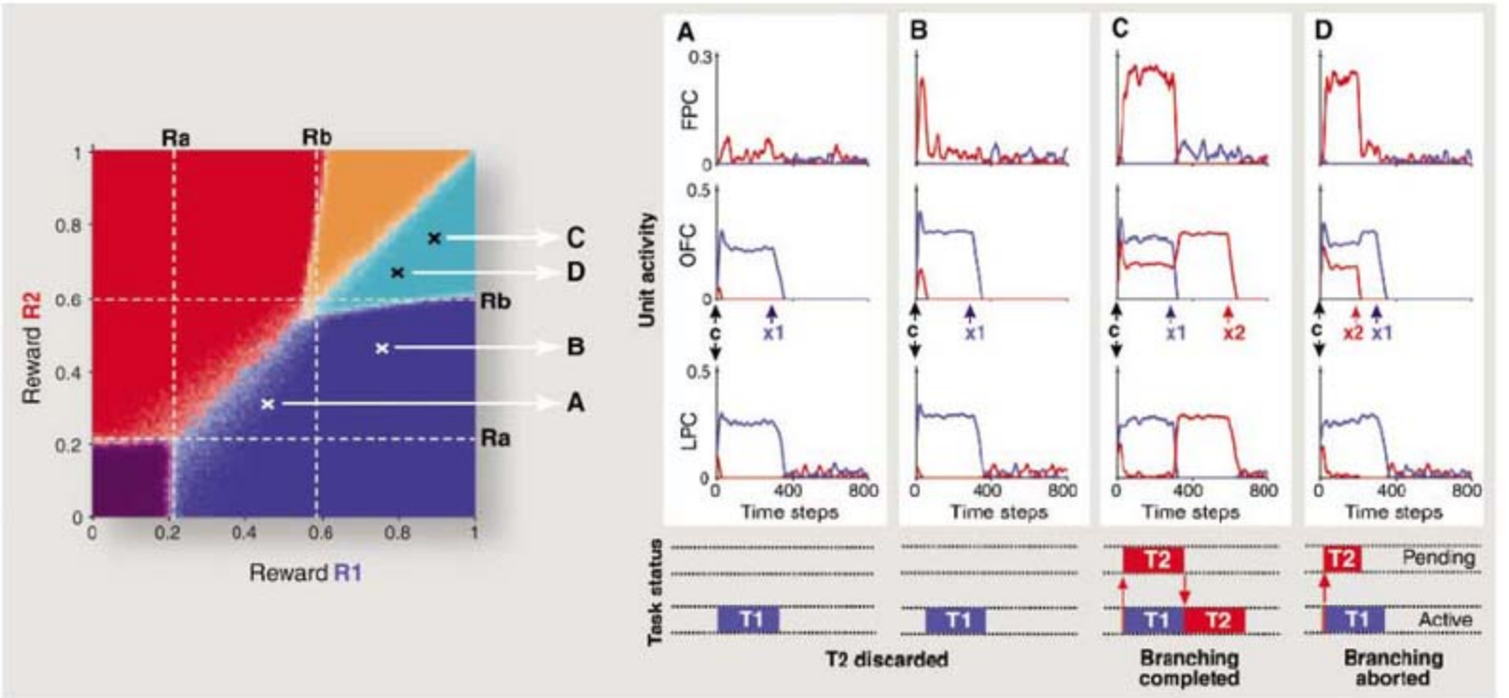

Fig. 3. Phase diagram and activation dynamics in the frontopolar model. Task sets are cued by an external cue, C, at time 0. **(Left)** Phase diagram showing different model behaviors according to the reward value (R1 and R2) expected from the two most rewarding task sets, T1 and T2, once cue C occurs. R1 and R2 remain unchanged until the occurrence of feedback signals X1 and X2, respectively. The phase diagram exhibits two reward thresholds, *Ra* and *Rb*, delimiting five regions with distinctive behaviors. The phase diagram is symmetrical, so that we describe only the regions where R1 > R2. **(Right)** (A, B, C, and D) show typical time courses of *Fpc*, *Ofc*, and *Lpc* neuron activity for each region corresponding to values R1 and R2 shown on the phase diagram (points A, B, C, and D in the left panel). Horizontal and vertical axes represent time and neuron activity, respectively. Blue and red lines show neuron activity coding for T1 and T2, respectively. (Purple region) R1 and R2 are not large enough (<*Ra*) for the network to select and encode any task sets. No tasks are executed. (Blue region) R2 is not large enough (<*Rb*), and no branching occurs. Only the most rewarding task set, T1, is encoded in *Lpc* for guiding current behavior (active status). All other task sets are discarded. In (A) and (B), expected reward R1 drops below *Ra* once feedback X1 occurs, terminating T1 execution. T2 remains unselected after T1 termination, although R2 becomes larger than R1 (a new external cue would be required for selecting T2). Note in (B) the phasic *Fpc* response to cue C, because R1 and R2 are close to threshold Rb. (Cyan region) R2 is large enough (>*Rb*) so that T2 is encoded in *Fpc* and placed in a pending state, whereas T1 is encoded in *Lpc* for guiding current behavior. (C) Expected reward R1 drops below *Rb* once feedback X1 occurs, whereas R2 is still above *Rb*. T1 is terminated and automatically replaced by T2 in *Lpc* for guiding subsequent behavior. Cognitive branching has occurred. (D) As in (C), except that R2 drops below *Rb* before R1 (X2 occurs before X1). As a result, the pending task set, T2, is discarded from the *Fpc*. T1 remains the active task set guiding behavior. Cognitive branching is aborted.

problem-solving. However, we suggest that the FPC function is restricted to the processing of simple cognitive branching, whereby only a single task can be maintained in a pending state at any one time. This hypothesis places severe serial and recursive constraints on human reasoning, problem-solving, and complex decision-making. Consistent with this view, it appears unlikely that the human brain has evolved to solve complex problems such as deciding the next move in a game of chess. Selective pressure to survive in a physically challenging environment may place other demands before the need for such higher cognitive faculties. Nevertheless, a capacity-limited FPC function may have endowed humans with two key adaptive advantages: on the one hand, an ability to pursue long-term behavioral plans and at the same time respond to demands of the physical or social environments; on the other hand, to explore any potential gain from the interposition of new task sets within ongoing behavioral routines or from the contingent recombination of previously established behavioral plans, as in genetic recombination mechanisms. Thus, the frontopolar cortex may have played an even more critical role in the gradual formation of complex behavioral and cognitive routines such as tool use in individuals and societies, that is, in human creativity rather than complex decision-making and reasoning.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5850/594/DC1
SOM Text
Figs. S1 and S2
References

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REVIEW

Social Decision-Making: Insights from Game Theory and Neuroscience

Alan G. Sanfey

By combining the models and tasks of Game Theory with modern psychological and neuroscientific methods, the neuroeconomic approach to the study of social decision-making has the potential to extend our knowledge of brain mechanisms involved in social decisions and to advance theoretical models of how we make decisions in a rich, interactive environment. Research has already begun to illustrate how social exchange can act directly on the brain's reward system, how affective factors play an important role in bargaining and competitive games, and how the ability to assess another's intentions is related to strategic play. These findings provide a fruitful starting point for improved models of social decision-making, informed by the formal mathematical approach of economics and constrained by known neural mechanisms.

Our lives consist of a constant stream of decisions and choices, from the everyday (will I respond to this e-mail?) to the highly consequential (will I have a child?). Essentially, the study of decision-making attempts to understand our fundamental ability to process multiple alternatives and to choose an optimal course of action, an ability that has been studied by various disciplines with different theoretical assumptions and measurement techniques, although with relatively little integration of findings.

The emergence of an interdisciplinary field, popularly known as neuroeconomics (*1*, *2*), has begun to redress this lack of integration and offers a promising avenue to examine decision-making at different levels of analysis. Its proponents seek to better understand decision-making by taking into account cognitive and neural constraints, as investigated by psychology and neuroscience, while using the mathematical decision models and tasks that have emerged from economics.

Most experimental studies of decision-making to date have examined choices with clearly defined probabilities and outcomes, such as choosing between monetary gambles. Given that we live in highly complex social environments, however, many of our most important decisions are made in the context of social interactions, which are additionally dependent on the concomitant choices of others—for example, when we are deciding whether to ask someone on a date or entering a business negotiation. Although relatively understudied, these social situations offer a useful window into more complex forms of decisions, which may better approximate many of our real-life choices.

As part of the neuroeconomic approach, researchers have begun to investigate the psychological and neural correlates of social decisions using tasks derived from a branch of experimental economics known as Game Theory. These tasks, though beguilingly simple, require sophisticated reasoning about the motivations of other players. Recent research has combined these paradigms with a variety of neuroscientific

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methods in an effort to gain a more detailed picture of social decision-making. The benefits of this approach are twofold. First, neuroscience can describe important biological constraints on the processes involved, and indeed, research is revealing that many of the processes underlying complex decision-making may overlap with more fundamental brain mechanisms. Second, actual decision behavior in these tasks often does not conform to the predictions of Game Theory, and therefore, more precise characterizations of behavior will be important in adapting these models to better fit how decisions are actually made.

Game Theory

Game Theory (*3*) is a collection of rigorous models attempting to understand and explain situations in which decision-makers must interact with one another. It offers a rich source of both behavioral tasks and data, in addition to well-specified models for the investigation of social exchange.

A common criticism of economic models is that observed decision behavior typically deviates, often quite substantially, from the models' predictions. Most classical game theoretical analyses predict that rational, self-interested players will make decisions to reach outcomes, known as Nash equilibria (*4*), from which no player can increase his or her own payoff unilaterally. However, players rarely play according to these strategies [see (*5*) for a useful summary of the primary findings in this field]. In reality, decision-makers are generally less selfish and strategic than the model predicts and value social factors such as reciprocity and equity. Nonetheless, the well-characterized tasks and formal modeling approach offered by Game Theory provides a useful foundation for the study of decisions in a social context. Although the rules of these games are typically simple, these tasks produce a surprisingly varied and rich pattern of decision-making.

One focus of Game Theory is strategic bargaining behavior; the Ultimatum Game (UG) (*6*) is often used to examine responses to fairness. In the UG, two players must divide a sum of money, with the proposer specifying this division. The responder has the option of accepting or rejecting the offer. If the offer is accepted, the sum is divided as proposed. If it is rejected, neither player receives anything. If people are motivated purely by self-interest, the responder should accept any offer and, knowing this, the proposer will offer the smallest nonzero amount. However, this Nash equilibrium prediction is at odds with observed behavior, and the modal offer is a 50/50 split. Further, low offers of less than 20% of the total amount are rejected about half of the time (*6*). Thus, people's choices in the UG do not conform to a model in which decisions are driven by financial self-interest, and neuroscience has begun to offer clues as to the mechanisms underlying these decisions.

Reciprocal exchange has also been studied extensively in the laboratory, exemplified by the Trust Game (TG) and the Prisoner's Dilemma. In the first (*7*), a player (the investor) must decide how much of an endowment to invest with a partner (the trustee). Once transferred, this money is multiplied by some factor, and then the trustee has the opportunity to return money to the investor, but, it is important to note, need not return anything. If the trustee honors trust and returns money, both players end up with a higher monetary payoff than the original endowment. However, if the trustee abuses trust and keeps the entire amount, the investor takes a loss. As the investor and trustee interact only once during the game, Game Theory predicts that a rational and selfish trustee will never honor the trust given by the investor. The investor, realizing this, should never place trust in the first place, and so will invest zero in the transaction. Despite these grim theoretical predictions, a majority of investors do in fact send some amount of money to the trustee, and this trust is generally reciprocated.

The standard Prisoner's Dilemma game (PDG) (*8*) is similar, except that both players simultaneously choose whether or not to trust each other, without knowledge of their partner's choice. In the PDG, payoffs depend on the interaction of the two choices. The largest payoff to the player occurs when he or she defects and the partner cooperates, with the worst outcome when the decisions are reversed (player cooperates while partner defects). Mutual cooperation yields a modest payoff to both players, whereas mutual defection provides a lesser amount to each. The Nash equilibrium for the PDG is mutual defection, a worse outcome for both players than mutual cooperation, but again, in most iterations of the game, players exhibit more trust than expected, with mutual cooperation occurring about 50% of the time.

Finally, coordination games (*9*) offer insights into how we assess the preferences of others and choose accordingly. For example, in matching pennies, players choose between two alternatives (heads or tails). One player wins if the two choices are the same, and the other wins if they are different. Players typically approach this game by attempting to infer the strategy of the opponent, thus providing a window into how we use intention-detection processes to assist our strategic decision-making.

Current Research Directions

Researchers have sought to investigate brain function in human subjects as they interact with other people in real, consequential social scenarios (e.g., by playing bargaining, reciprocal exchange, and coordination games with partners). Although this approach is a relatively recent endeavor, several interesting themes have emerged in current research: (i) social reward; (ii) competition, cooperation, and coordination; and (iii) strategic reasoning.

Social reward. Neuroeconomic research tries to illuminate the process by which we encode decision outcomes and how this might, in turn, guide our future choices. It is widely hypothesized that the brain uses a common-reward metric, which is crucial for a system to choose between rewards delivered in different modalities. A strong candidate for this metric is the mesolimbic dopamine system, and single-cell recordings from neurons in the striatum, a major projection site of midbrain dopamine cells (see Fig. 1), have shown that neural responses scale reliably with reward magnitude (*10*). These results also are observed in humans, with activity changes in the striatum scaling directly with the magnitude of monetary reward or punishment (*11*, *12*). In simple coordination games, researchers have uncovered compelling evidence for the existence of reinforcement-learning mechanisms in nonhuman primates (*13*, *14*). This mechanism is thought to improve choices over time, by continually updating the outcomes according to the rewards and punishments encountered in the environment.

Building from this basic research, researchers have discovered that the human striatum appears to be centrally involved in social decisions, above and beyond any financial outcome that may

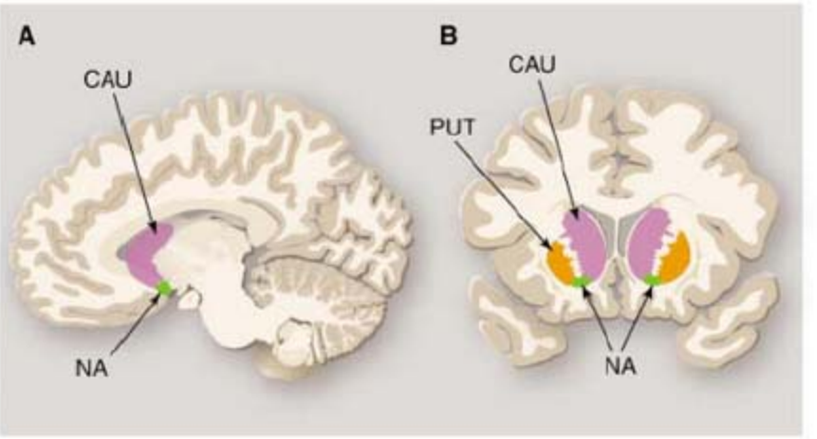

Fig. 1. The subcomponents of the striatum, involved in the processing of reward. **(A)** Sagittal section and **(B)** coronal section illustrate the location of the caudate nucleus (CAU), putamen (PUT), and nucleus accumbens (NA).

accrue to the player. Several neuroimaging studies have demonstrated that the striatum tracks a social partner's decision to reciprocate or not reciprocate cooperation, appearing to encode abstract rewards such as the positive feeling garnered by mutual cooperation. Reciprocated cooperation with another human leads to increased activation in the striatum as compared with a control condition where an identical amount of money is earned, whereas unreciprocated cooperation shows a corresponding decrease in activation in this area (*15*). In addition, activation is associated with increased cooperation in subsequent rounds, which suggests that the striatum may register social prediction errors to guide decisions about reciprocity.

Related findings have been reported in a multiround TG (*16*), where activation in the trustee's caudate was related to how much reciprocity the investor had shown on previous trials, and thus corresponded to an "intention to trust" signal of the trustee. Further, this signal gradually shifted in time—in early trials the signal occurred after the investor made his or her choice, whereas later on, this signal occurred much earlier, before the investor's decision was revealed. This temporal shift is also reminiscent of reward prediction errors in reinforcement learning models (*17*).

These prediction error signals from partner decisions can be greatly reduced when decisions are based on prior information. Providing general personality profiles of partners before they play a TG led to reduced caudate activity when responding to partners described in either positive or negative moral terms, although responses to morally neutral players remained unchanged (*18*). This suggests that prior beliefs can reduce the amount of trial-by-trial learning, which demonstrates both top-down and bottom-up influences on the neural basis of social cooperation.

Of course, social reward need not always be related to positive, mutually cooperative, actions. Players also may derive satisfaction from punishing defectors, even when this punishment leads to a financial loss to the player. This was illustrated in a positron emission tomography study (*19*) where investors were confronted with nonreciprocators in a TG. Players had the option to punish these defectors, though this also entailed a loss of points for themselves. Nonetheless, players made the decision to punish, and this was associated with activation in the caudate, with activation greater when the punishment was real (involving a financial loss to the defector) than when it was merely symbolic.

Finally, two recent studies have examined the neural basis of social altruism in tasks where players must decide whether to donate money to charitable organizations. In one study (*20*), the striatum was engaged by both receiving money and by donations to charity. In another (*21*), these areas were also activated by receipt of money and by observing a donation to a charity, but this activation was enhanced when this charitable donation was voluntary as opposed to forced. The latter studies are intriguing and offer the possibility of extending investigations of social reward beyond simple two-player interactions to interactive decision-making at a societal level, which has potential implications to inform questions of public policy.

Competition, cooperation, and coordination. In addition to the rewarding or punishing effects of social interactions, these scenarios have also illustrated the prominent role emotions play in social decision-making. Classical models of decision-making have largely ignored the influence of emotions on how decisions are made, but recent research has begun to demonstrate the powerful effect these factors play.

Emotional processes seem to reliably engage a set of structures including reward-processing mechanisms discussed above and areas of the midbrain and cortex to which they project, such as ventromedial prefrontal cortex (VMPFC), orbitofrontal cortex, and anterior cingulate cortex, as well as other areas such as the amygdala and insula (*22*) (see Fig. 2). Early pioneering work in this domain showed that patients suffering damage to VMPFC who presented with associated emotional deficits were impaired in performing gambling tasks (*23*), which demonstrated experimentally that emotion plays a vital role in determining decisions.

In terms of social decision-making, negative emotional states are observed behaviorally as a result of both inequity and nonreciprocity, such as unfair offers in a UG (*24*). These emotional reactions have been proposed as a mechanism by which inequity is avoided and may have evolved precisely to foster mutual reciprocity, to make reputation important, and to encourage punishment of those seeking to take advantage of others (*25*). Indeed, even capuchin monkeys respond negatively to unequal distributions of rewards by refusing to participate in a task that requires effort if they witness another monkey receiving equal reward for less work (*26*).

Neuroscientific studies offer the potential to go beyond speculation to examine the causal relationship between an emotional reaction and subsequent social decision, as well as to investigate whether areas specialized for the processing of basic emotions may be co-opted for more complex affective reactions. A functional magnetic resonance imaging study (*27*) examined unfair behavior in the UG and found brain areas, primarily the anterior insula, that exhibited greater activation as the unfairness (i.e., inequity) of the offer increased. Further, this area was more active when the subject was playing with another human than when engaged with a computer partner. It is noteworthy that the activation of this area predicted the player's decision to either

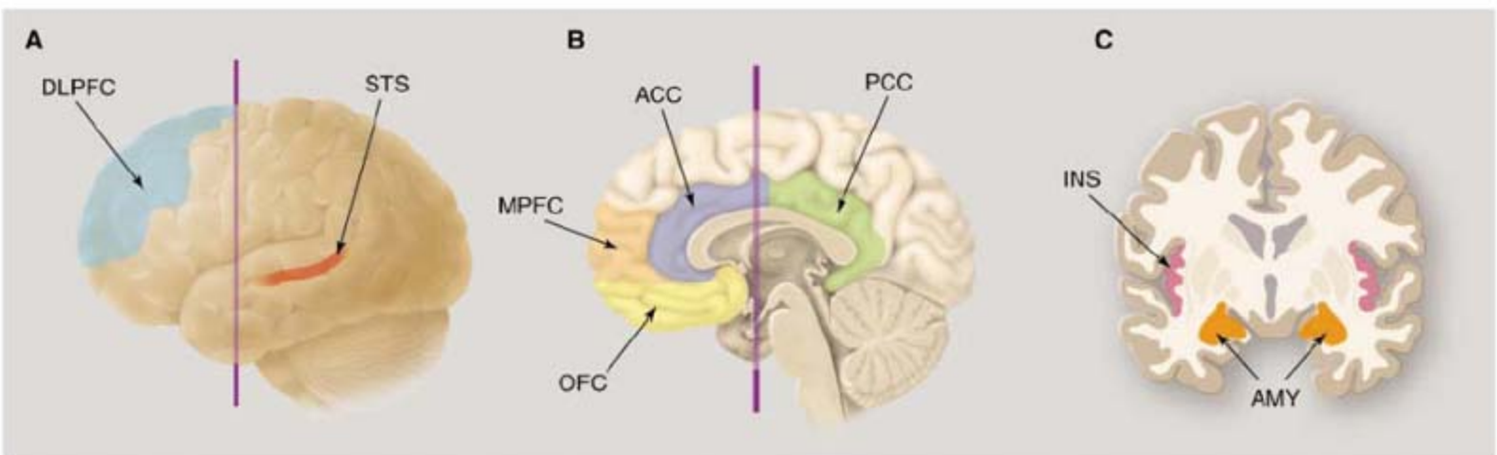

Fig. 2. Map of brain areas commonly activated in social decision-making studies. **(A)** The lateral view shows the location of the dorsolateral prefrontal cortex (DLPFC) and superior temporal sulcus (STS). **(B)** The sagittal section shows the location of the anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), and posterior cingulate cortex (PCC). **(C)** The coronal section [cut along the purple line in (B)] shows the location of the insula (INS) and amygdala (AMY). Areas circled are those often associated with ToM processes.

accept or reject the offer, with rejections associated with significantly higher activation than acceptances. In a related study, this area was also active in an iterated PDG (*28*), where individuals with a stronger anterior insula response to unreciprocated cooperation showed a higher frequency of defection. Finally, the same region has been found in relation to empathic responses when witnessing a fair PDG partner's receiving painful electric shocks (*29*).

The presence of anterior insula activations in these studies is particularly interesting as this brain region is also responsive to physically painful (*30*) and disgusting (*31*) stimuli and is involved in mapping physiological states of the body, including visceral sensations of autonomic arousal (*32*). Anterior insula and associated emotion-processing areas may play a role in marking a social interaction as aversive and, thus, discouraging trust of that partner in the future.

Separate measures of emotional arousal provide support for this hypothesis. An UG study measuring skin-conductance responses, used as an autonomic index of affective state, found higher skin conductance activity for unfair offers, and as with insular activation, this measure discriminated between acceptances and rejections of these offers (*33*). Finally, both VMPFC patients (*34*) and normal players primed with negative emotional states (*35*) reject unfair offers more frequently than controls in both cases, further evidence that regulation of affective processing is important in social decision-making.

In a similar vein to the suppression of striatal activation by frontal, "top-down" processes in reward studies, activation of frontal regions to unfair offers in UG studies has been interpreted as a mechanism by which other more deliberative goals (such as reputation maintenance or the desire to make money) can be implemented. Transcranial magnetic stimulation was used to disrupt processing in dorsolateral prefrontal cortex while players were making decisions about offers in an UG (*36*, *37*). In both studies, stimulation increased acceptance rates of unfair offers as compared with control situations, which provides strong evidence for a causal relation between activation in this area and social decisions.

A final potentially fruitful avenue of research in cooperative and competitive games is in using neuropeptides such as oxytocin, which is known to facilitate social affiliation in nonhuman animals, to modulate human social relationships. In a TG (*38*), intranasal administration of oxytocin led to an increase in trust placed by investors. This effect was not general for all types of decisions and was not observed for risk or in games with random outcomes, but rather was specific for consequential social interactions with other humans.

Although this research has greatly increased our understanding of the neural correlates of social decisions, it also has the potential to inform economic theories. Recent models in behavioral economics have attempted to account for social factors, such as inequity aversion, by adding social utility functions to the standard models [e.g., refs. (*39*, *40*)]. Modeling these functions based on the underlying neural patterns provides a useful constraint in the development of new models.

Strategic reasoning: Theory of mind. An ancillary benefit of these social decision-making tasks is that they can offer insight into how we process the intentions and actions of others, an ability often termed Theory of Mind (ToM). Studies of ToM reveal a network of areas that appear to be involved in this ability, primarily medial prefrontal cortex and anterior paracingulate cortex (*41*, *42*), and decision-making studies have similarly demonstrated activation in these regions when players are immersed in thinking and acting on the beliefs of others, either by guessing partner strategies (*43*) or when comparing play with another human to play with a random device, such as a computer partner (*44*, *45*). This suggests that these regions may be involved in "intention detection," that is, assessing the meaning of behavior from another agent.

Clearly, other areas may be involved in these ToM processes, such as the tempo-parietal junction (*46*), and it is also intriguing that these proposed areas largely overlap with those of the brain's purported "default network" (*47*). Although this integration is not well understood at present, use of social decision tasks offers potentially interesting avenues to uncover exactly how and where we process the meaning behind actions. For example, a recent study (*48*) uncovered neural activation arranged spatially along the anterior cingulate cortex corresponding to either "me" or "not me" responses in a Trust Game. These activations were only observed in the presence of a partner, which suggests that they were involved in encoding the social aspects of the exchange.

Additionally, some individuals with psychiatric disorders such as autism spectrum disorder have demonstrated severe ToM deficits. Autistic participants had a more difficult time shifting strategy in PDG and also were more likely to accept initial low UG offers (*49*), which demonstrated shortfalls in the ability to reason successfully in real social interactions.

Conclusion

The preceding sections review some general ways in which experimental economics and neuroscience can be combined to make important new contributions to understanding social decision-making. These findings provide some traction for measuring physical mechanisms responsible for social decision-making and offer the promise of identifying and precisely characterizing both the mechanisms and the factors that influence their engagement and interaction. Games offer some real advantages over standard decision-making paradigms, not least in their embedding in actual, consequential, social interactions that allow investigation of complex processes such as reputation, trust, equality, and cooperation.

As with any novel approach, there are challenges to address. The component disciplines operate at different levels of analysis and have different theoretical assumptions. More practically, there are important differences in methodology, in particular, with regard to the use of deception, generally prohibited by economics but used extensively in psychology and neuroscience. In addition, it is important to use caution in interpreting neural activations as measured by neuroimaging. For example, the association of a brain region with either value encoding or aversive processing in previous studies does not necessarily mean that activation in this area in the context of an interactive game can automatically be interpreted as rewarding or punishing, respectively. It would therefore be prudent for the field, as a whole, to buttress these claims by either converging evidence from other methodologies or, at the very least, demonstrating behavioral performance in line with the neural predictions, such as a player's preference for options that activate reward centers more strongly (*19*).

The neuroeconomics of individual decision-making has had some notable success in investigating how parameters of decision utility are represented in the brain (*50*–*52*). In a similar vein, the neuroeconomics of social decision-making could probe whether there are neural correlates of parameters that Game Theory both predicts (such as knowledge of payoffs and long-term strategic thinking) and does not predict (such as affective biases and individual differences in ToM ability). In addition, data generated by this approach can prove valuable in providing additional constraints, based on the neural substrate, for any theory that seeks to accurately model social decision-making.

Finally, the neuroscientific endeavor could also profit from allying more closely with the formal models of Game Theory, as opposed to merely viewing it as a useful source of tasks. For example, modeling of behavior in these tasks (*53*) can yield useful insights as to the decision-making behavior of organisms over time and could help illuminate processes that different games may have in common.

It would also be useful to explore ways in which the various economic approaches may make contact with more traditional neuroscientific frameworks, such as the reinforcement learning models mentioned above. Do the computations described by these models map onto the formal Game Theory analysis?

The ability to better understand how our decisions will affect others—and their decisions

affect us—has relevance from the broadest levels of public policy to our most immediate interpersonal interactions. There is little doubt that the combination of Game Theory tasks, with their formal, detailed mathematical models, and the techniques of modern neuroscience offers fruitful opportunities for the study of social decision-making. This approach can both advance the predictive accuracy of theoretical models by constraining them based on behavioral performance and the underlying neurobiology, as well as further our knowledge of how people make decisions in a social context.

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REVIEW

Decision-Making Dysfunctions in Psychiatry—Altered Homeostatic Processing?

Martin P. Paulus

Decision-making consists of selecting an action from a set of available options. This results in an outcome that changes the state of the decision-maker. Therefore, decision-making is part of a homeostatic process. Individuals with psychiatric disorders show altered decision-making. They select options that are either non-optimal or nonhomeostatic. These dysfunctional patterns of decision-making in individuals with psychiatric disorders may fundamentally relate to problems with homeostatic regulation. These may manifest themselves in (i) how the length of time between decisions and their outcomes influences subsequent decision-making, (ii) how gain and loss feedback are integrated to determine the optimal decision, (iii) how individuals adapt their decision strategies to match the specific context, or (iv) how seemingly maladaptive responses result from an attempt to establish an unstable homeostatic balance.

Before considering what goes wrong with decision-making in psychiatric patients, it is useful to summarize some of the basic conceptualizations and findings regarding decision-making in general. Generically, decision-making is selecting an action from a set of available options, which may result in an outcome that leads to a different psychological and physiological state of the decision-maker. Decision-making consists of a complex set of processes that are orchestrated in various brain systems to find an optimal outcome. Optimal decision-making requires a set of higher-order cognitive functions by which individuals regulate their actions, thoughts, and emotions according to current psychological or physiological states, goals, and environmental conditions. In particular, individuals must be able to appraise the momentary status of their needs. Therefore, decision-making is part of a homeostatic process. Homeostasis can be defined as a dynamic physiological, cognitive, and affective steady state (*1*) that integrates multiple bottom-up sensory afferents and top-down cognitive and affective control processes, resulting in dynamic stability (i.e., resistance to internal and external perturbations). Decisions maintain or bring individuals into a new homeostatic state. Temporally, decision-making can be divided into three stages (*2*): (i) the assessment and formation of preferences among possible options, (ii) the selection and execution of an action (and the inhibition of alternative actions), and (iii) the experience or evaluation of an outcome. Initially, a value or utility is assigned to each available option (*3*), which determines the preference structure of the decision-making situation. The brain must evaluate not only what is occurring now but also what may or may not

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occur in the future (*4*). The current state of the individual, the time to experience an outcome, the degree to which the outcome is advantageous, and the likelihood that an outcome will be observed are important variables that determine this preference structure. The decision-maker incorporates previous outcome-related information, action-related information, and contextual or situational information to select an action. Each of these factors has to be considered in the context of the homeostatic balance of the individual to better understand decision-making dysfunctions in psychiatric-disorder populations.

Traditional approaches to understanding decision-making are based on economic theory (*5*) and mathematical choice psychology (*6*). Several investigators have augmented this approach to include affective or visceral factors (*7*–*9*), which profoundly affect the preference structure of available options. Individuals often underappreciate, hardly remember, and have difficulty explaining the influence of these factors (*8*). Nevertheless, the effect of these factors is consistent with the emerging understanding of how the brain computes decisions as derived from systems-neuroscience approaches (*10*–*12*) and neurobiologically informed theories (*13*, *14*). For example, the somatic-marker hypothesis (*15*) posits that options are tagged with positive and negative somatic states to guide individuals in making optimal choices (*16*). Thus, there is growing evidence that decision-making and homeostatic processing are inextricably linked (*17*) and that dysfunctions of decision-making cannot be understood without the reference to changes in homeostasis.

The inclusion of visceral factors (*8*) and affect heuristics (*7*) as part of decision-making has moved this process from a rational selection of options based on preference structures into the realm of homeostatic maintenance behaviors. One cannot separate decision-making from the current state of the individual (*6*) and/or understand decision-making dysfunctions in psychiatric patients without delineating how the disorder affects homeostasis. This view highlights an important but experimentally often underappreciated aspect of decision-making: that is, the interoceptive valuation of available options and the general role of interoceptive neural systems in decision-making. Interoception refers to the homeostatic sensing of the internal state of the body (*1*). This process combines the limbic sensory representation of subjective "feelings" within the anterior insula and the limbic motor representation of volitional agency within the anterior cingulate as the neuroanatomical basis for all human emotions (*18*). In this framework, affective/visceral processes are not simply occasional events but are ongoing and continuous, which is critical for the notion that visceral factors influence decision-making (*8*).

Two recent neuroimaging studies provide strong support for the homeostatic nature of decision-making. First, the preference structure in

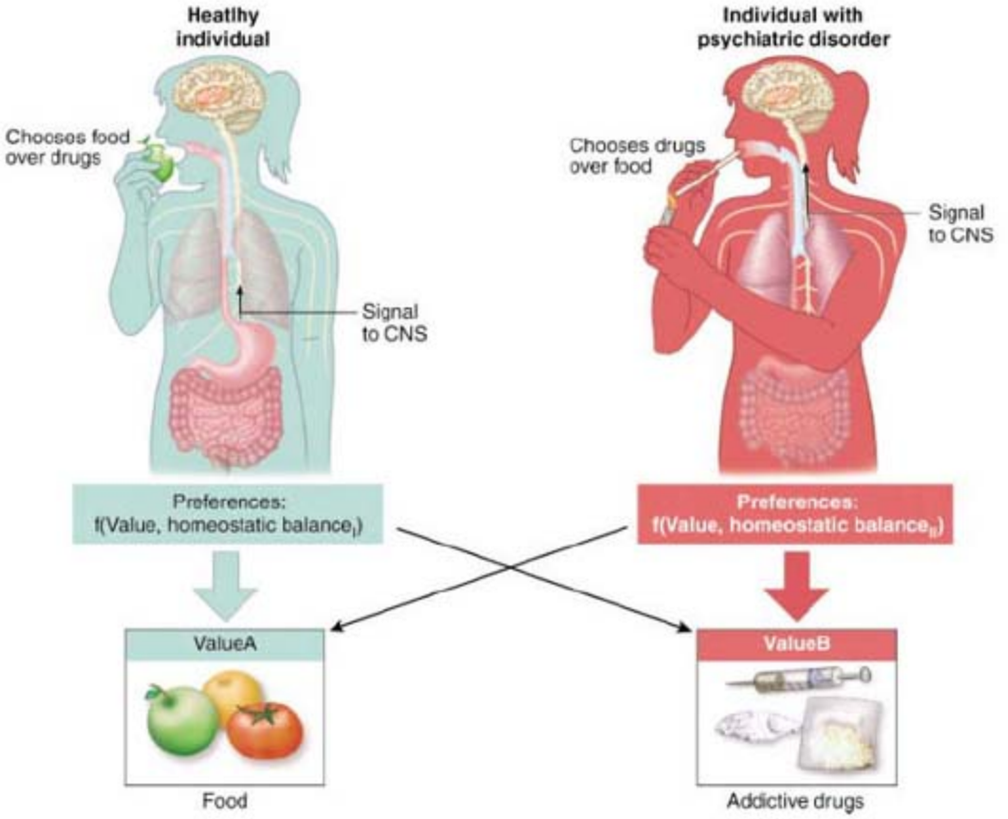

Fig. 1. Schematic illustration of two individuals who are in a different homeostatic balance in relation to each other (a person who is hungry and about to eat on the left and a person who is about to use methamphetamine on the right). It is presumed that interoceptive information transmitted via C-fibers and integrated in the anterior insular cortex plays a pivotal role in instantiating the current homeostatic balance. As a consequence, the value of an option (fruits on the left, methamphetamine on the right) is transformed via a complex function *f*, which takes into account probabilities and reward magnitudes but also the interoceptive state, into a different set of preferences based on the current status of the individual. The central hypothesis put forth here is that individuals with psychiatric disorders do not necessarily value the options differently in themselves but establish a different preference structure (represented by the thickness of the arrows pointing toward the options) based on their altered homeostatic balance.

repeated decision-making situations is fundamentally affected by the sampling of the available options. An individual who makes a decision needs to determine strategically whether to gather or to exploit option-related information. There is evidence that cortical and subcortical systems compete to moderate this conflict and balance the individual toward exploratory and exploitative action strategies (*19*). Second, a fundamental observation in classical choice psychology is that the value of an option is relative to a contextual reference point (the so-called "framing effect"). Limbic processing areas, which are also critically involved in homeostatic maintenance behaviors (such as the amygdala), are important for this effect, and top-down modulatory areas (such as the medial prefrontal cortex) can predict the susceptibility to the framing effect (*20*).

Homeostatic Processes in Psychiatric Disorders

Decision-making dysfunctions in individuals with psychiatric disorders are most likely due to several different alterations of component processes. These alterations may be due to a primary processing dysfunction (for instance, an altered contribution of outcome magnitude, probability, or delay to computing the preference structure) or to a secondary dysfunction resulting from a primary dysregulation of the homeostatic balance. Although many investigators have argued the former, here I argue that decision-making dysfunctions in psychiatry are largely consequences of homeostatic dysregulation (Fig. 1). This approach is similar but not identical to the allostasis model (*21*)—the notion that a disease process is a result of the continued attempt to achieve stability—which has been proposed for addiction. Here, homeostasis is not a simple bottom-up determined physiological set point, but rather a bottom-up and top-down determined dynamical state. Therefore, the altered assessment and formation of preferences, the suboptimal selection and execution of an action, and the attenuated or exaggerated experience or evaluation of an outcome are hypothesized to be due to compensatory processes, albeit dysfunctional, aimed to bring the individual into a homeostasis. As a

consequence, the valuation of options changes the preference structure in different disorder populations. This homeostatic formulation of decision-making dysfunctions has important implications. First, it asserts that in many cases primary processing of the preference structure is intact, which is consistent with the finding that decision-making dysfunctions are often absent in asymptomatic individuals. Second, seemingly irrational decision-making may be adaptive and explicable within the context of attempting to maintain homeostasis. For example, increased risk-taking in substance-using individuals is often referred to as nonadaptive. However, studies of risk-sensitive foraging show that the degree of risk is a function of the homeostatic balance of the animal or individual (*22*, *23*). For example, the frequency of visiting artificial flowers containing high-variance rewards is directly related to the degree to which foraging birds find themselves in a precarious energy balance. Thus, increased risk-taking may represent an adaptive mechanism of the drug-using individual. Third, this approach calls for experimental modulation of the homeostatic equilibrium during decision-making experiments with psychiatric populations to determine whether dysfunctional decision-making can be remedied.

Specific Examples of Dysfunctional Decision-Making in Psychiatric Populations

Substance-use disorders. Various deficits in decision-making have been reported in people with substance-use disorders (*24*). Specifically, these individuals do not appropriately take into account outcomes that occur sometime in the future versus those that occur now, and they therefore discount delayed rewards at significantly higher rates than do comparison subjects (*25*–*27*). Some have argued that this behavior occurs because of an underlying disposition of impulsivity rather than a substance-induced problem (*28*). This presumes a discounting model of impulsiveness (*29*) (impulsivity is a direct consequence of an increased attenuation of rewards as a function of delay), which is supported by the finding that the degree of temporal discounting is correlated with ratings of impulsivity (*30*). Thus, altered discounting may be a predisposing characteristic but not a consequence of years of substance use, because individuals reporting illicit drug use at a younger age tend to discount the value of future hypothetical rewards more steeply than do their peers (*31*).

Individuals with substance-related problems, irrespective of the substance used, perform poorly on the Iowa gambling task (IGT) (*32*–*36*), which measures the degree to which individuals select small immediate gains associated with long-term gains (advantageous option) over large immediate gains associated with long-term losses (disadvantageous option). These decision-making problems occur with and without concomitant working memory or executive-functioning problems, suggesting that decision-making is not simply a result of impairments in executive functioning. Individuals with alcohol-related problems also perform worse on this task (*37*). Addicted individuals either show attenuated learning of selecting advantageous options or do not choose preferentially advantageous options over disadvantageous ones. It is not clear which behavioral processes or neural systems are responsible for this deficit. In one study, a κ-antagonist, buprenorphine, improved performance on the IGT in opiate-dependent subjects relative to methadone-maintained individuals, which points toward an opioid mechanism (*38*). Both predisposing characteristics and consequences of use (i.e., duration of abstinence, years of abuse, number of relapses, and times in treatment) predict these performance deficits (*39*). However, it is not clear whether these deficits are related to abnormal orbitofrontal functioning, a consequence of years of drug use, related to poorer outcomes, or even generalizable to other decision-making situations.

Substance users also exhibit altered decision-making on other tasks. Amphetamine abusers select suboptimally when presented with low-probability options and deliberate longer before making their choices (*40*). As opposed to healthy volunteers, outcome success does not modulate changes in win-stay/lose-shift strategies in methamphetamine-dependent individuals (*41*). Cocaine-dependent individuals show related but not identical abnormalities on different decision-making tasks (*42*). Taken together, there is substantial evidence for altered behavioral decision-making in substance-using individuals, irrespective of the behavioral probe that was used. These dysfunctions include altered processing of future outcomes, reduced ability to adapt to short- versus long-term gains, selection of suboptimal choices based on probability, and/or reduced ability to incorporate outcomes into altering the preference structure of available options. Nevertheless, it is not yet clear whether these dysfunctions are due to primary differences in establishing the preference structure of the available options or, alternatively, represent an attempt to generate a preference structure that is optimal for an individual with an altered homeostasis.

In decision-making neuroimaging studies, methamphetamine-dependent individuals show altered fronto-parietal activity during "hard" decisions, which may point to inefficient cortical processing (*43*). We found less decision-making–related activation in the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortex, the anterior cingulate cortex (ACC), and the parietal cortex (*41*, *44*) in these subjects. Cocaine users show greater activation during performance of the IGT in the right OFC but less activation in the right dorsolateral and left medial prefrontal cortex, which may reflect differences in the anticipation of reward and/or planning and working memory (*45*). These altered brain-activation patterns may be the consequence of an imbalance between an impulsive, amygdala system for signaling pain or pleasure of immediate prospects and a reflective, prefrontal cortex system for signaling pain or pleasure of future prospects (*46*). Others have pointed out that an altered link between affect and decision is the key to understanding decision-making dysfunctions in substance-using individuals (*47*).

Are changes in decision-making behavior (and associated brain functions) a result of a preexisting characteristic, which may predispose subjects to use drugs and become dependent on them, or a consequence of years of use? Two complementary approaches have been used to examine this question. First, a high-risk population of individuals who have not yet developed substance dependence can be assessed to determine whether decision-making dysfunction predates the consequences of years of use. Second, acute effects of abused drugs on decision-making processes can be used to gauge whether acute administration of these substances has the potential to alter such processes.

Increased risk-related behaviors have been observed in "high-risk" populations (*48*). Individuals who use stimulants but are not dependent select risky responses more frequently than do comparison subjects, but the nondependent stimulant users also select risky choices less often after punishment. This risk-taking behavior correlates with measures of sensation-seeking and impulsivity but not with other personality measures, anxiety, or a tendency toward using alcohol (*49*). In these individuals, an increase in caudate nucleus activation during a simple decision-making paradigm aimed to determine the influence of outcome uncertainty is correlated with impulsivity (*50*). Thus, those at risk show altered decision-making and brain-activation patterns before developing substance dependence. Ultimately, however, the continued use of substances despite adverse consequences that lead to dependence may have additional effects on the brain and behavior.

Acute administrations of drugs with abuse potential have shown effects on decision-making behavior that are not completely consistent with those observed in substance-using individuals. The stimulant methylphenidate reduces risk-taking behavior in healthy volunteers (*51*), amphetamine [and in some (*52*) but not other (*53*) studies, alcohol] attenuates the delayed discounting curves (*54*), and acute administration of (±)3,4-methylenedioxymethamphetamine increases the degree to which the previous stimulus influences the selection of the current response (*55*). Neither the benzodiazepine diazepam (*56*) nor cannabinoids altered impulsive behavior (*57*), but these drugs have been shown to increase risky decision-making (*58*, *59*). Taken together, the results from acute administration studies are only partially consistent with findings in substance-dependent individuals. Thus, decision-making dysfunctions and associated altered neural-

substrate processing could reflect a behavioral- and neural-systems biomarker to identify high-risk individuals. However, much more work is needed to better delineate the altered homeostatic processes that give rise to the behavioral- and neural-systems dysfunctions before one can begin to use this approach as an endophenotype for substance-use disorders.

Mood and anxiety disorders. Reward processing is part of assessing the value of options and occurs during the first stage of the decision-making process. Altered reward processing has been implicated in the basic pathophysiology of depression. Depressed patients show less activation in bilateral ventral striatal activation, which is believed to be involved in reward processing. This, in turn, has been shown to correlate with decreased interest and/or pleasure in the performance of activities (*60*), but not with levels of anxiety (*61*). Individuals with major depressive disorder (*62*) and bipolar disorder (*63*) also perform more poorly on the IGT. These findings have been replicated in a related but experimentally different decision-making task for manic and depressed patients (*64*). As compared to healthy subjects, bipolar individuals during a manic episode are more sensitive to feedback and switch more frequently during high–error rate conditions (*65*). Thus, those suffering from mood disorders present decision-making dysfunctions characterized by assigning different values to available options, probably because of reward-processing abnormalities in the ventral striatum.

Uncertainty is an important component of decision-making, and cognitive models of generalized anxiety disorder highlight the role of intolerance of uncertainty (*66*). Accordingly, decision-making by anxious subjects is influenced to a greater extent by ambiguous stimuli (*67*). Moreover, the sensitivity of high-trait anxious individuals to infrequent errors is associated with increased activation in the ACC and the medial prefrontal cortex (*68*). Finally, the intolerance of uncertainty is positively related to the degree of ACC activity (*69*). These results may be related to the sensitivity of anxious individuals to interoceptive sensations. These bodily sensations are associated with the assessment of available options as dangerous or threatening (*70*), a process that may be mediated by altered anterior insula functioning (*71*). In particular, risky options that are associated with uncertain and possible aversive outcomes may invoke more aversive anticipation of negative consequences, which could result in reduced numbers of risk-taking behaviors. Not surprisingly, increased activation in the anterior insular cortex is related to reduced risk-taking and increased neuroticism or harm avoidance (*72*, *73*), which are temperamental characteristics of individuals prone to develop anxiety disorders. Therefore, increased sensitivity to possible aversive outcomes during the assessment stage of decision-making because of hyperactivity in both the anterior cingulate and the anterior insular cortex may be a key feature of anxiety disorders. From a homeostatic perspective, anxious individuals find themselves in a state that is characterized by increased top-down modulation of bottom-up interoceptive afferents that heighten sensitivity to and bias interpretation toward aversive outcomes.

There is substantial evidence of orbitofrontal pathology in individuals with obsessive compulsive disorder (OCD) (*74*). Some (*75*), but not others (*76*), find impaired decision-making on the IGT in OCD patients to be associated with greater error-related activation in the rostral ACC, which is correlated with symptom severity (*77*). Although the behavior of OCD individuals is sensitive to changing contingencies, these people show decreased responsiveness in the right medial and lateral OFC, as well as in the right caudate nucleus during outcome processing (*74*). These individuals may experience an altered processing of reward history and valuation of options because of the relative disconnect between the dorsolateral, orbitofrontal, and anterior cingulate cortices with limbic regions (especially the amygdala) and with the basal ganglia (*78*).

Schizophrenia. Surprisingly, several studies have shown that individuals with schizophrenia perform normally on the IGT (*79*). Both first-episode and chronic schizophrenic patients take longer than controls to make decisions, and both groups are also impaired on a measure of risk adjustment. This impairment is more severe in the chronic patients than in first-episode patients (*80*). Decision-making dysfunctions in schizophrenia subjects may be due to an intermittent disruption of decision-strategies, which leads to choice patterns that can be both highly predictable and highly unpredictable (*81*–*83*). This pattern is particularly evident in deficit, but not in nondeficit, schizophrenia patients (*84*). Brain-imaging studies of decision-making show that the bilateral parietal cortex in schizophrenic patients is more involved in the assessment of uncertainty and less involved in success-related processing (*85*). Overall, evidence for experimental decision-making dysfunctions in schizophrenia is more mixed than that for other disorders. This may be due to inadequate experimental assessment or to the heterogeneity of the population characterized as being schizophrenic. The experimental findings are clearly at odds with a growing literature on the reduced capacity to make decisions using questionnaire approaches (*86*). Future investigations will need to develop experimental paradigms that can better probe the components of impaired decision-making capacity.

Future Directions

Decision-making is a complex process that engages numerous neural systems to optimally select an option. There is clear evidence of dysfunctional decision-making in psychiatric populations. However, many of the studies have so far used a limited number of behavioral tasks, which are complex and probe multiple decision-related processes. Several approaches will be necessary to gain a deeper and disease-relevant understanding of such dysfunctions. First, instead of one decision-making task, a set of behavioral paradigms will need to be developed to probe different aspects of decision-making and to provide converging validity of some of the proposed decision-making constructs. Second, clinical populations need to be better defined, sampled across sites, and examined using multilevel descriptions to better delineate the specificity of the dysfunction, relation to the clinical syndrome, and degree to which decision-making dysfunctions are preexisting characteristics or consequences of the disorder or treatment. Third, decision-making will need to be examined within the homeostatic context of the individual. It is not yet clear whether dysfunctional decision-making in individuals with psychiatric disorders is a consequence of altered assessment, execution, or evaluation stages of decision-making, or whether it is adequate decision-making in the context of an altered homeostatic balance. Fourth, neuroimaging laboratories will need to collaborate with clinical researchers to better delineate the neural substrates involved in disorder-related decision-making dysfunctions. Fifth, systems and theoretical neuroscientists will need to work with clinical researchers to develop novel computational hypotheses and examine their relevance in making meaningful predictions. For example, a specific aberrant computational process has been suggested to underlie learning and discounting dysfunctions in a recent addiction model (*87*). However, this model needs to be tested in various populations of substance-using individuals and refined to make clinically useful predictions. Nevertheless, the experimental study of decision-making provides an opportunity for meaningful interdisciplinary approaches that can help to reveal how brain processes go awry in individuals with psychiatric disorders.

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REVIEW

Decision Theory: What "Should" the Nervous System Do?

Konrad Körding

The purpose of our nervous system is to allow us to successfully interact with our environment. This normative idea is formalized by decision theory that defines which choices would be most beneficial. We live in an uncertain world, and each decision may have many possible outcomes; choosing the best decision is thus complicated. Bayesian decision theory formalizes these problems in the presence of uncertainty and often provides compact models that predict observed behavior. With its elegant formalization of the problems faced by the nervous system, it promises to become a major inspiration for studies in neuroscience.

Evolutionary psychology has found that many human behaviors can be well understood assuming adaptation of psychology to the past social environment of humans [e.g., (*1*)]. Similarly, ethology, the study of animal behavior [e.g., (*2*)], has shown that many of the properties of the nervous system and the bodies of animals are remarkably well adapted to their ecological niche. These disciplines have shown that, over the course of evolution, animals are often endowed with solutions to common problems that are close to optimal [(*1*), but see (*3*)]. Many studies in neuroscience analyze low-level processes. For example, researchers study how animals control their limbs, how they infer events in the world, and how they choose one of several possible rewards. Such processes may have remained conserved for very long periods of time. We can thus expect the solution used by the nervous system for such problems to be close to optimal.

Normative models formalize how the idea of adaptation predicts properties of the nervous system. These models assume that a process has

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an objective (e.g., walk using least energy). Such an objective is typically formalized by a function ("utility") that defines how good the solution is (e.g., the energy used). By combining the utility function with constraints (e.g., properties of muscles), it is possible to derive the best possible solution to the problem, usually using computer simulations. If the prediction of the model is matched by biology, it is concluded that, indeed, we have understood the purpose of a system. Normative models thus ask the "why?" question and formalize the ultimate purpose of a system. In this review, I focus on normative approaches to decision making; the nervous system often comes up with near-optimal decisions in a world characterized by uncertainty. To understand the nervous system, descriptive knowledge of how the nervous system works should be combined with normative knowledge of which problems it solves.

Decision Theory

The purpose of the central nervous system is to make decisions so that we can thrive by interacting successfully with our environment (Fig. 1A). When we play darts, we need to decide which position on the dartboard to aim at (Fig. 1B). The dartboard assigns a score to any possible dart position and thus defines the outcome. The objective of playing darts is to obtain as many points as possible. Within decision theory, such an objective is called a utility function [e.g., (*4*)]. A utility function $U(outcome)$ measures how good or bad any possible decision outcome is. If dart players could choose where the dart will hit the board, they would choose the position that yields the most points and would thus maximize utility.

Although we can freely make decisions, we cannot directly choose the decision outcomes. If we always aim for the same position a, say the center of the bull's eye, and throw many darts, we will produce a distribution of dart positions, x, on the dart board (Fig. 1C, inset). Within decision theory, this probability distribution is denoted $p(outcome = x|decision = a)$. If we aim at the position on the board that gives the highest score, we may instead hit a neighboring area of the dartboard and receive a low score. Depending on the position we aim at, different scores become more or less likely. This is a special case of a general problem in decision theory: Outcomes depend on decisions in a probabilistic way.

To derive the most beneficial decision, it is necessary to combine the utility function with knowledge of how our decisions affect potential outcomes. The expected utility is

$$E[Utility(decision)] \equiv \sum_{\substack{possible \\ outcomes}} p(outcome|decision)\,U(outcome)$$

The best decision is then defined as the one that will maximize the expected utility (*5*).

The decision theoretic approach can be used whenever we know how decisions are related to outcomes and we know the utility of the outcomes. We can apply this framework to the example of darts playing. If we had low motor noise, we would be best off aiming at the triple 20 (Fig. 1C). In contrast, if we have a realistic value of motor noise, the best point at which to aim is not the point of maximal score but is to the lower left of the board (Fig. 1D, marked by dart). Both the behavior of advanced amateur players who have moderate motor variance and the behavior of professional players who have low motor variance are predicted by this decision theoretic approach. A range of recent studies of decision-making have analyzed situations that are analogous to playing darts (*6*). Such simple decisions are well predicted from the assumption that people solve their decision problems in a fashion that is close to optimal. The approach also applies to many animal behaviors: Animals need to choose to forage or rest, fight or flight, continue moving or freeze in place. Moreover, any behavior of an animal is, in some abstract way, a decision. The nervous system chooses one behavior from the set of all possible behaviors. Decision theory is thus a fundamental formalization of many problems that are solved by the nervous system and studied in neuroscience.

A number of recent studies, under the umbrella name of neuroeconomics, have started to analyze how the nervous system represents and computes with a utility function (*7*–*9*). Because utility is central to any decision, it is important to understand how the nervous system represents reward. Utilities are important for the nervous system because it uses them to act successfully. It has been shown that the nervous system represents changes in expected utility in a way predicted by a major learning theory, reinforcement learning (*10*). Traditionally simple rewards, such as monetary or food incentives, are used in experiments that analyze how the nervous system represents utilities. However, insights from evolutionary biology (*1*) predict that many different factors will influence the utility of decisions. Indeed, it has been shown that the nervous system exhibits a reward signal when someone else who cheated in a game is punished (*11*). Future research will have to uncover the full complexity of how utility functions are represented and used by the nervous system.

Bayesian Statistics

Deciding seems easy: Choose the action that is associated with the highest expected utility. However, the probability of an outcome given the decision is difficult to estimate. To do so, we need to predict how the world will change until the outcome and how any decision would affect the world. This prediction can only be probabilistic because we have uncertainty about the properties of the world, stemming, for example, from noisy perception (*12*).

Bayesian statistics defines how uncertain pieces of information may be combined into a

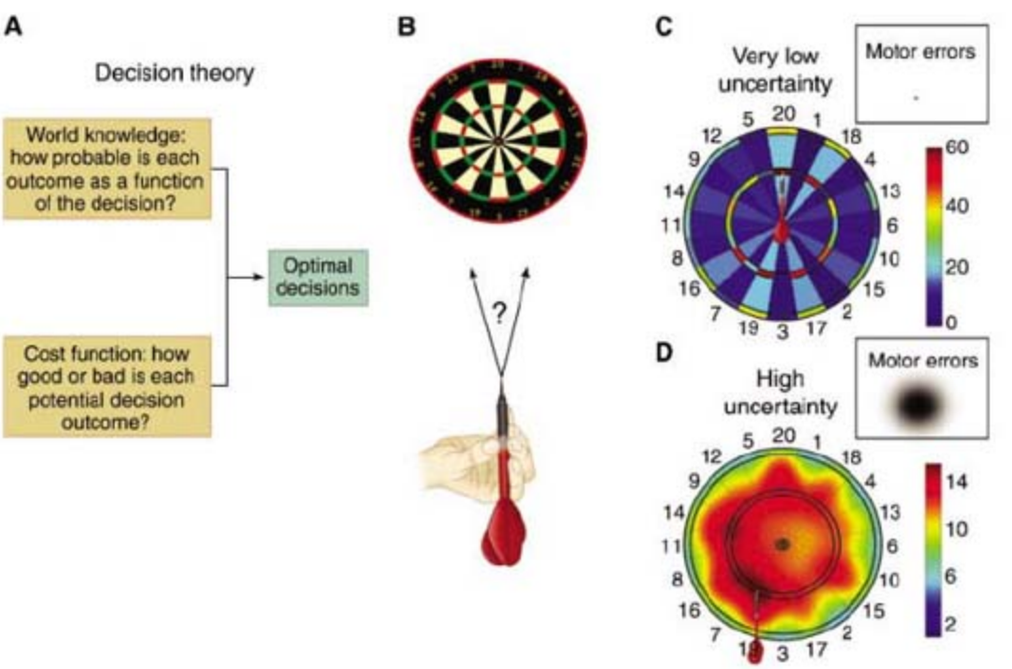

Fig. 1. Decision theory. **(A)** To make optimal decisions, we need to combine what we know about the world with our utility function measuring how good or bad potential outcomes are. **(B)** In the example of playing darts, we need to decide where to aim. **(C)** As a function of the aiming point, the expected score is shown for an unbelievably good darts player with almost no movement errors. **(D)** As in (C) but for a mediocre darts player with large motor errors.

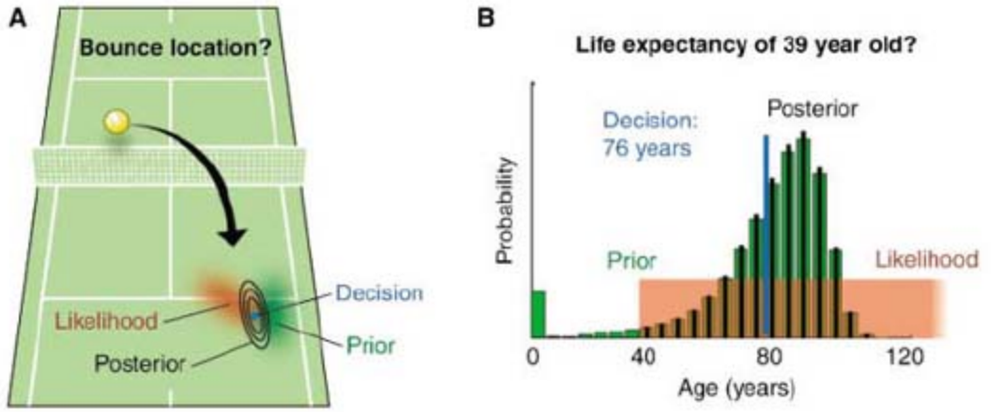

Fig. 2. (A) In the example of tennis, people need to combine what they know from before (prior, green) with what they currently see (likelihood, red). That way we can estimate the posterior (black contour lines) to make an optimal perceptual decision (blue). **(B)** Similarly if we estimate the life expectancy of a person who is 39 years old, we need to combine what we know from before (prior, histogram of lifetimes, green) with our new information (person survived 39 years, likelihood, red) to come up with an optimal estimate.

joint estimate. New information (called a likelihood) needs to be combined or integrated with information from the past (called a prior). Similar problems occur when information from several cues, for example, proprioceptive and visual, needs to be combined into a joint estimate. Bayesian decision theory (*13*), the use of Bayesian statistics in a decision framework, defines how our beliefs should be combined with our utility function. Because most if not all of our decisions are made in the presence of uncertainty, understanding the way the nervous system deals with uncertainty is central to understanding its normal mode of operation.

Integration of priors and likelihoods. To calculate the probabilities of outcomes, it is often necessary to update our belief from the past (prior) with new knowledge (likelihood). For example, when we play tennis it is helpful to estimate where the ball will land. The visual system, although noisy, still provides us with an estimate or a likelihood of where the ball will land (sketched in red in Fig. 2A). This knowledge may be combined with information obtained from experience; the positions where the ball may land are not uniformly distributed over the court. The locations may be clustered near the boundary lines, where it is most difficult to return the ball. This distribution of positions is called the prior (sketched in green in Fig. 2A). Bayes's rule states that how the probability of the ball landing at position x given our observation o (posterior) needs to be estimated as

$$\underbrace{p(x|o)}_{\text{posterior}} = \underbrace{p(x)}_{\text{prior}}\,\underbrace{p(o|x)}_{\text{likelihood}}/p(o)$$

Recent studies have analyzed such combinations in simple integration problems. Sensorimotor integration, force estimation, timing estimation, speed estimation, the interpretation of visual scenes, just to name a few, have been analyzed (*14*, *15*). Together, these studies demonstrate that people intuitively combine prior knowledge with new evidence in a way predicted by Bayesian statistics.

Bayesian methods also apply to decision-making in cognitive contexts (*16*). What would be your guess of the life expectancy of a 39-year-old? People can use two sources of information to answer this question. They may use the prior, the distribution of lifetimes (Fig. 2B, green). They may also use the likelihood, this person must have survived the first 39 years of his or her life (Fig. 2B, red). With Bayes's rule, we can combine these two pieces of information, just as in the example of tennis (Fig. 2B, black). We thus estimate a life expectancy of about 76 years (using the negative square error as the utility function). Human participants exhibit cognitive behaviors that are close to optimal predictions. The same approach has been used to successfully predict human estimates for many other everyday cognition problems (*16*). People incorporate knowledge about the probability distributions into estimates in a fashion that is predicted by Bayesian decision theory.

Cue combination. Estimation will often depend on two different cues. For example, we may see and feel an object and use both senses to infer the properties of the object. Bayesian statistics allows us to solve these problems with the same mathematical framework used for the combination of prior and likelihood. A couple of recent studies have examined how subjects solve such cue combination problems. For example, the combinations of visual and auditory information and visual and tactile information, as well as within modality cue combination (e.g., texture and disparity), have been studied. In such cases, cues are combined in a fashion that is close to the optimum prescribed by Bayesian statistics (*14*, *15*, *17*, *18*).

Although there is strong evidence that animals represent their degree of uncertainty and

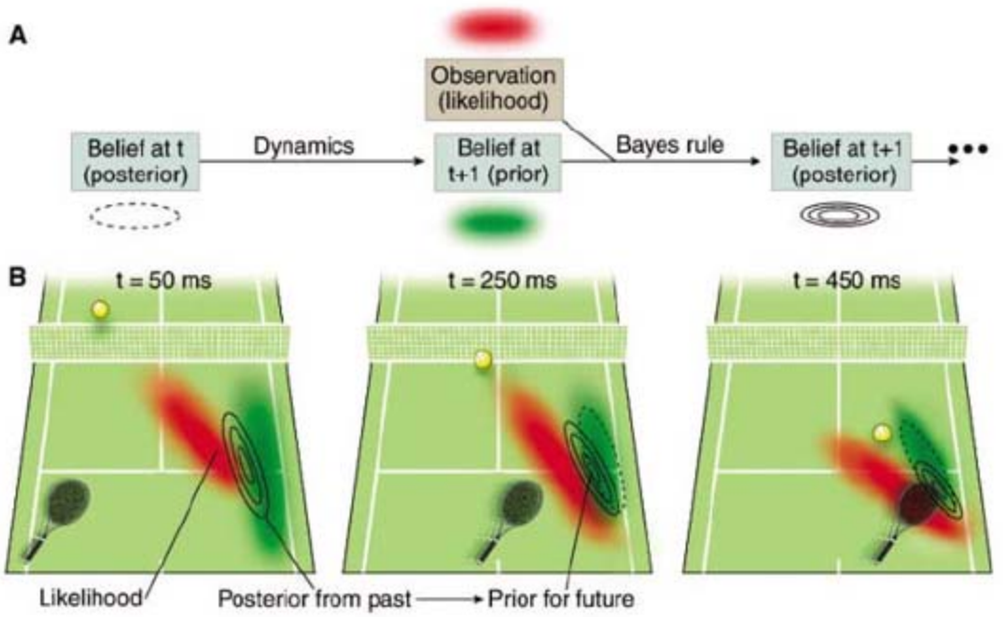

Fig. 3. Integration of information over time. **(A)** A diagram of a Kalman filter is shown. At any point of time t, the person has a belief about the state of the world. The person then updates this belief with a model of the dynamics of the world (e.g., gravity) to calculate the belief at the next point of time. This belief (prior) is then combined with new sensory information (likelihood) using Bayes's rule to calculate the belief at the next time step. The ellipses indicate probability distributions sketched in (B). **(B)** To estimate the position of a ball hitting the ground, people continuously update their beliefs with incoming sensory information, yielding precise estimates. The posterior of the previous time step is the prior for the new one: The dashed line indicating the previous posterior is identical to the one standard deviation line of the prior (green).

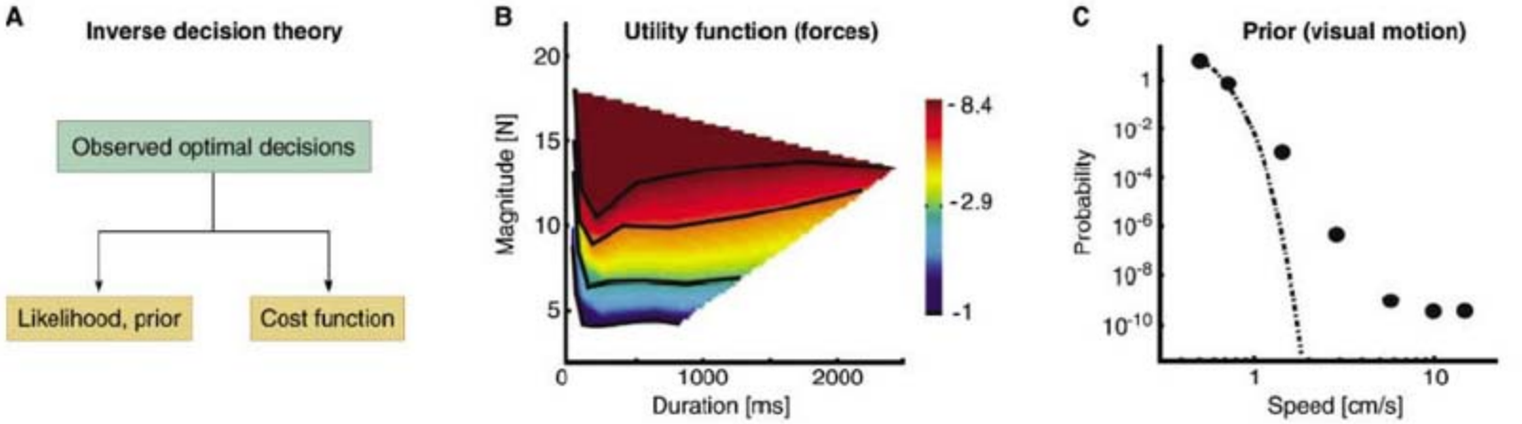

Fig. 4. Inverse decision theory. **(A)** In inverse decision theory, it is assumed that people behave optimally. From a sequence of optimal behavior, the priors, likelihoods, and utility functions people use are inferred through various computational methods. **(B)** In motor control, the utility function of producing forces of varying duration and magnitude have been calculated. **(C)** For visual decisions, people assume that small velocities are much more likely than large velocities.

combine different pieces of information into a joint estimate, there is still relatively little known about how the nervous system implements such computations. Recently, a couple of theoretical studies proposed how the nervous system may represent probabilities and combine them into estimates (*19*, *20*). What is exciting about these studies is that they make clear testable predictions of how the nervous system may represent uncertainty. Understanding this representation is key for neuroscience because animals essentially make all their decisions in the presence of uncertainty.

Integration of information over time. The state of the world and our information about it is continually changing. In the example of tennis, we only used an estimate at a single point of time. In reality, tennis players continuously observe the ball's motion, updating their beliefs about the position where the ball will land in a continuous manner. The Kalman filter formalizes how such a process may work. The filter uses knowledge about the dynamics of the world to convert its belief about the state of the world at the previous instance of time into a belief at a future point in time. For example, in the tennis game we expect the ball to move because of its forward momentum and to accelerate because of gravity. The resulting belief (prior, Fig. 3, green) is then combined with new sensory information (likelihood, Fig. 3, red) to produce an updated belief (posterior, Fig. 3, ellipses). This way the Kalman filter updates its beliefs over time. In the case of playing tennis, such a strategy predicts that, as the ball flies, our estimate of the landing position will progressively be updated and usually become more precise. It is thus possible to make an efficient decision in situations that change continuously over time.

A range of recent studies have probed the strategies used by human participants in such situations. The way that people estimate the position of their hand in the dark is well predicted by Kalman filtering (*21*). Similarly, when people balance a pole they also seem to use such strategies (*22*). Moreover, the way the nervous system represents changing muscle properties can be understood by assuming a Kalman filtering strategy (*23*, *24*). These studies demonstrate that when people integrate information over time to make simple sensorimotor decisions, they seem to do so in a fashion that is consistent with the optimal Bayesian solution.

The nervous system constantly integrates information over time, and a range of new studies analyzed how it does so (*25*). In many such experiments, one of two stimuli is given, for example either a stimulus that moves to the right or a stimulus that moves to the left. If the stimulus is sufficiently noisy, the nervous system needs to integrate information over an extended period of time to make a good decision. Neurons were found that exhibit activities that correlate with the predicted process of optimal information integration over time. The nervous system takes into account probabilistic knowledge of potential rewards when integrating evidence for decision-making (*26*). The resulting models are particularly useful because they have a normative component (optimal integration of evidence) while having a straightforward descriptive component (neurons can integrate inputs over time).

Inverse Decision Theory

If people make decisions optimally, the mechanism of decision theory may be inverted: Computational techniques [e.g., (*27*)] are used to infer which priors, likelihoods, and utility functions the participants used to make their decisions. For example, a utility function with a few free parameters may be proposed, and the parameters may be fit to human behavior. Experimental economics (*28*) has extensively asked which utility functions people are optimizing. Only recently has the study of neuroscience and low-level decision-making started asking which priors are used and which utility functions are optimized.

Many studies in neuroscience analyze motor control, an area where decision-making is key. For example, would you rather carry a 2-kg weight for 1 min or a 1-kg weight for 2 min? We intuitively make repeatable choices in such situations that are of relevance to everyday life. Such a utility function was recently inferred by using inverse decision theory (*29*) (Fig. 4A). This utility function is highly nonlinear in force magnitude and duration and is more complicated than previously proposed utility functions (*30*). This highlights a problem in decision theory: Frequently, good fits to behavior may be obtained with wrong utility functions. Inverse decision theory can thus be seen as a way of searching for violations of the assumptions made when building a decision theoretic model.

The framework of inverse decision theory also allows the analysis of which priors and which likelihoods are used by people. Studies indicate that people underestimate the speed of visual motion (*31*). This has been argued as the result of using a Gaussian prior for interpreting that low speeds are most likely. But why should people use a Gaussian distribution? We do not know which prior would be optimal in real life, although some recent progress in the statistics of natural scenes may lead that way (*32*). In a recent experiment, the prior used by human participants was measured by using inverse decision theory (*33*) (Fig. 4A). The prior is not Gaussian and is rather similar to an exponential function. This may inspire future experiments to characterize how the nervous system implements such a prior.

The strength of inverse decision theory in allowing for a wide range of possible utility functions is also its weakness. Inverse decision theory will always yield a utility function, likelihood, or prior for which the actually observed behavior is optimal. If the results differ from those assumed by a previous decision theoretic model, we can falsify this model. However, the

results should only be the basis of a new model if we can understand (and test) how the inferred functions derive from properties of the world. Similar problems also appear in other decision theoretic models that do not explicitly use inverse decision theory. The theoretician may fiddle with the decision theoretic model, trying different utilities, likelihoods, and priors, until there are good fits to human performance. As in all other models that explain data, overfitting is also a problem for decision theoretic models.

Inverse decision theory allows for the estimations of the used utility functions, priors, and likelihoods, which may alleviate the search for their neural representation. For example, if we know how utility functions depend on ideas of fairness when playing games, it is possible to search for brain areas that represent this aspect of the utility function (*11*). Searching for the neural representation of a utility function that has been proposed on theoretical grounds, but is irrelevant for human behavior, may miss important aspects of decision-making. When searching for the representation of priors or utility functions in the nervous system, it seems central to know the form of the priors and utility functions that are actually used by human participants.

Discussion

The world is complicated, and consequently so is deciding. Models in neuroscience typically analyze simple relationships between variables. However, at least our high-level behavior is characterized by structural relationships. Events in the world have causes, and we naturally interpret events in terms of cause and effect. A few studies of Bayesian statistics over the past couple of years have started to address the issue of how people may be able to infer the structure of the world (*34*, *35*). Structure implies that not only features but their relationships play a fundamental role. This concept has long been at the heart of cognitive science. How people solve complicated real-world problems needs to be understood. A lot of recent progress in machine learning aims at inferring the structure of the world from real data (*36*), a process that people perform effortlessly. The study of decisions in neuroscience can draw upon advances in machine-learning to make interesting new predictions.

The decision theoretic approach may be limited in several ways. Humans should behave suboptimally for ethologically new kinds of decisions that are not repeated enough to allow for learning [but see (*37*)]. This may, for example, be relevant to the way people participate in lotteries (*38*). Using Bayes's rule to combine pieces of information is the best mathematical solution to any information combination problem and thus always has been the best solution. Similarly, moving efficiently has always been beneficial to animals. The simple low-level properties of neural decision-making should thus be expected to be close to optimal.

Decision theory formalizes how animals should decide and thus does not directly make predictions of how the nervous system should implement the algorithm leading to such decisions (*39*). Countless different implementations may lead to the same optimal decision rules. However, the normative approach is not limited to decision theory. There may equally be costs and benefits to implementing algorithms in various ways. For example, having many long connections between neurons may use volume and energy and lead to slow information transmission. The idea of wiring length minimization explains well the placement of neurons in cortical maps (*40*) as well as within the body of the nematode *Caenorhabditis elegans* (*41*). Similarly, it may be argued that visual neurons should faithfully represent the world with the fewest spikes (least metabolic cost), an idea that predicts many properties of sensory representations (*42*). Normative ideas may even apply to cellular properties. The density of sodium channels in the squid giant axon may be understood from the idea that the squid giant axon should rapidly transmit action potentials used to allow the squid to flee from a predator (*43*, *44*). Normative models and decision theory in particular offer ways of formalizing important problems that the nervous system needs to solve. Models in neuroscience should seek to explain the wealth of available experimental data and also incorporate knowledge of the problem solved by the system.

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Amazon Forests Green-Up During 2005 Drought

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Large-scale numerical models that simulate the interactions between changing global climate and terrestrial vegetation predict substantial carbon loss from tropical ecosystems (*1*), including the drought-induced collapse of the Amazon forest and conversion to savanna (*2*).

Model-simulated forest collapse is a consequence not only of climate change–induced drought but also of amplification by the physiological response of the forest: Water-limited vegetation responds promptly to initial drought by reducing transpiration (and photosynthesis), which in turn exacerbates the drought by interrupting the supply of water that would otherwise contribute to the recycled component of precipitation (*2*). This physiological feedback mechanism should be observable as short-term reductions in transpiration and photosynthesis in response to drought under current climates.

We used satellites to observe whether an Amazon drought in fact reduced whole-canopy photosynthesis (*3*). The enhanced vegetation index (EVI) from the Terra satellite's Moderate Resolution Imaging Spectroradiometer (MODIS) is a composite of leaf area and chlorophyll content that does not saturate, even over dense forests. Properly filtered to remove atmospheric aerosol and cloud effects, EVI tracks variations in canopy photosynthesis, as confirmed by ecosystem flux measurements on the ground (*3*, *4*).

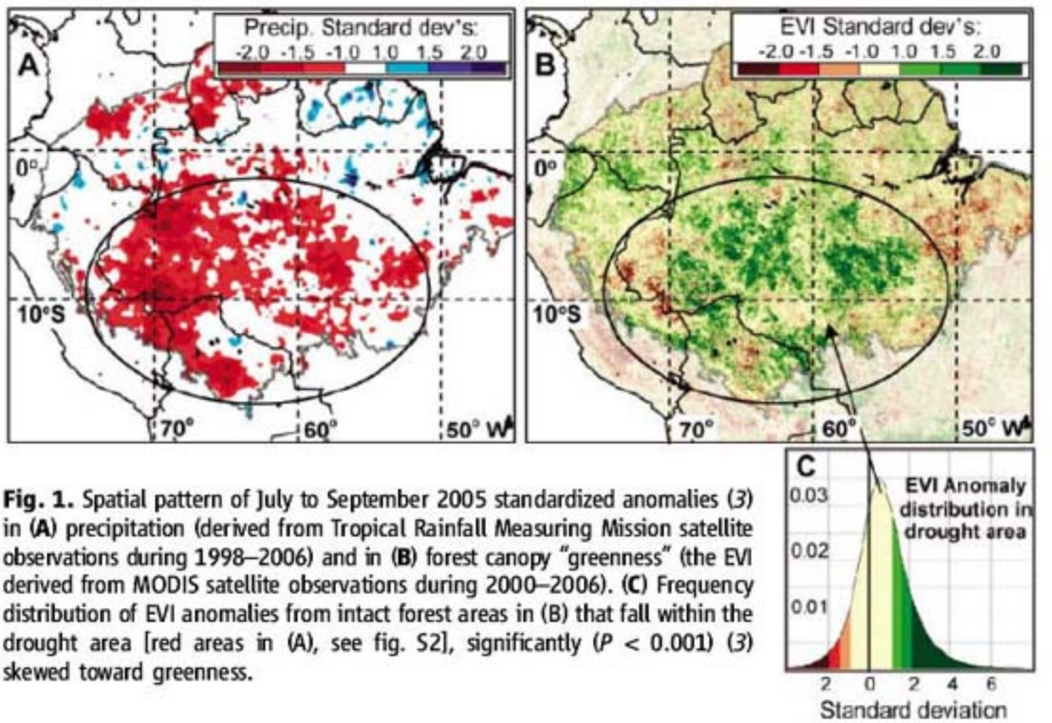

Fig. 1. Spatial pattern of July to September 2005 standardized anomalies (*3*) in (**A**) precipitation (derived from Tropical Rainfall Measuring Mission satellite observations during 1998–2006) and in (**B**) forest canopy "greenness" (the EVI derived from MODIS satellite observations during 2000–2006). (**C**) Frequency distribution of EVI anomalies from intact forest areas in (B) that fall within the drought area [red areas in (A), see fig. S2], significantly ($P < 0.001$) (*3*) skewed toward greenness.

A widespread drought occurred in the Amazon in 2005 (*5*), the first such climatic anomaly since the launch of the Terra MODIS sensor in 1999, providing a unique opportunity to compare actual forest drought response to expectation at large scales.

Drought intensity peaked during dry season onset (July to September), primarily in southwest and central Amazônia (Fig. 1A) [the drought's temporal evolution is depicted in (*5*)]. If drought had the expected negative effect on canopy photosynthesis, it should have been especially observable during this period, when anomalous interannual drought coincided with the already seasonally low precipitation. The observations of intact forest canopy "greenness" in the affection areas, however, are dominated by a significant increase ($P < 0.0001$) (*3*) not a decline (Fig. 1, B and C). Much of the smaller area exhibiting decline is heavily affected by human activity or consists of different vegetation types (fig. S2).

Increased greenness is inconsistent with expectation if trees are limited by water but follows from increased availability of sunlight (due to decreased cloudiness) when water is not limiting—if, for example, trees are able to use deep roots and hydrologic redistribution to access and sustain water availability during dry extremes (*6*, *7*).

These observations suggest that intact Amazon forests may be more resilient than many ecosystem models assume, at least in response to short-term climatic anomalies. This work does not alter the growing understanding of how Amazon forests are vulnerable to stressors such as deforestation and fire, a vulnerability observed to increase dramatically during the 2005 drought (*5*). But it does suggest that forest vulnerability to climatic effects alone needs to be carefully assessed with studies aimed at improving models by integration with observations. Especially important for future work are observations to address the critically important question of forest response to longer-term drought (*8*), such as may be induced by strong El Niño events or longer-term climate change.

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Outward Transport of High-Temperature Materials Around the Midplane of the Solar Nebula

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The Stardust samples collected from Comet 81P/Wild 2 indicate that large-scale mixing occurred in the solar nebula, carrying materials from the hot inner regions to cooler environments far from the Sun. Similar transport has been inferred from telescopic observations of protoplanetary disks around young stars. Models for protoplanetary disks, however, have difficulty explaining the observed levels of transport. Here I report the results of a new two-dimensional model that shows that outward transport of high-temperature materials in protoplanetary disks is a natural outcome of disk formation and evolution. This outward transport occurs around the midplane of the disk.

Observations of molecular clouds, the material from which planetary systems form, indicate that the silicates contained within are predominantly amorphous (*1*)—their atoms are randomly oriented with respect to one another. Thus, it is surprising that comets contain abundant crystalline silicates—grains whose atoms are arranged in ordered, repeating patterns (*2*, *3*). Because crystalline grains can form from amorphous precursors through processing at high temperatures (>1100 K) (*2*, *4*), it was suggested that these silicates originated in the hot, inner regions of the solar nebula and were transported outward beyond 15 to 20 astronomical units (AU), where long-period comets formed (*2*). This hypothesis is supported by the findings of the Stardust mission (*5*, *6*). Not only do the samples collected from Comet Wild 2 contain large amounts of crystalline Mg-rich olivine, but a refractory grain dubbed "Inti" has also been identified. This grain has mineralogy and oxygen isotope ratios similar to those of the calcium- and aluminum-rich inclusions (CAIs) found in chondritic meteorites, suggesting a common origin (*7*). CAIs record temperatures >1500 K and likely formed close to the Sun (*8*). Spectral signatures of crystalline grains in the cool, outer regions of disks around other stars (*9*, *10*) indicate that outward transport of high-temperature materials is a fundamental consequence of protoplanetary disk evolution.

Protoplanetary disks evolve as they drive mass inward to be accreted by their central stars (*11*). The mechanism responsible for this evolution is not well understood, but one popular hypothesis is that the transport arises due to a turbulent viscosity given by $\alpha c^2/\Omega$, where c is the local speed of sound, Ω is the local Keplerian angular frequency, and α is a parameter, <1, that characterizes the level of turbulence (*12*). The viscosity may be due to a process like the magnetorotational instability (MRI) (*13*), and when coupled with the differential rotation rates of a disk, generates shear stresses between neighboring parcels of gas. While these stresses drive mass inward, the turbulence allows materials to diffuse outwards. Numerical investigations (*3*, *14*) found that delivering crystalline grains to the comet-formation region in this manner is inefficient, because the inward flows associated with disk evolution frustrate the outward diffusion of particles. To deliver processed grains at high abundances (>10%) to the comet-formation region, the transport distance had to be small (a few AU). This meant that temperatures in the solar nebula had to exceed 1000 K out to 10 AU, which requires mass accretion rates $\sim 10^{-5}$ solar masses ($M_\odot$)/year (*3*). However, this value implies a short lifetime for the solar nebula, because a negligible fraction of its mass would remain after 10^6 years. This is inconsistent with the age differences between CAIs and chondrules in chondritic meteorites (*15*) and models of Jupiter's formation by core accretion (*16*), both of which indicate that the solar nebula retained a substantial amount of mass for >2 million years. Formation of the giant planets by disk fragmentation (*17*) is also problematic because these disks would be too hot to be gravitationally unstable.

These numerical studies used one-dimensional (1D) models for the solar nebula that tracked how the surface density of grains evolved due to the effects of diffusion, gas drag, and viscous flows. In these models, the motions due to gas drag and viscous flows are found by determining the characteristic (midplane) and net (vertically averaged) velocities, respectively, and applying them to all particles at a given radial distance from the Sun (*3*, *14*, *18*). In reality, the dynamics of solid particles in the solar nebula depended strongly on the values of the local gas volume density and pressure, as well as their respective gradients (*19*), all of which varied with height above the nebular midplane (Fig. 1). A major consequence of these variations is that the viscous stresses that developed within the nebula also varied with height, producing rapid inward flows along the surfaces (high altitudes) of the disk (*20*–*22*). The flow rates fell off at lower altitudes and, indeed, were directed outward around the midplane (Fig. 2).

To account for these effects, I have modeled particle transport in a viscous, two-dimensional (2D) protoplanetary disk. The model tracks the radial and vertical transport of solids due to diffusion, viscous flows, gas drag, and settling due to gravity (*23*). The 2D model reveals that outward transport in a viscous disk is much more efficient than found by 1D studies (Fig. 3). This increased efficiency is due largely to the ease with which particles are transported outward around the midplane, the reasons for which are twofold. First, outward diffusion of materials occurs more rapidly in regions of the disk that have negative density gradients. Second, particles that diffuse outward in this region do so without having to battle inward flows associated

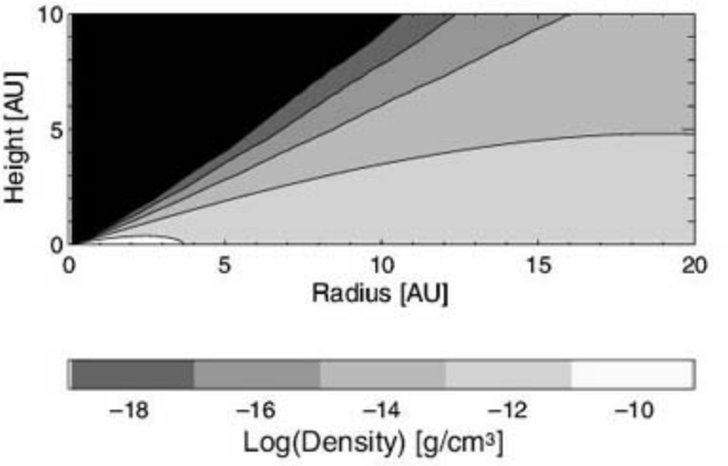

Fig. 1. Gas volume density contours for a disk in hydrostatic equilibrium whose surface density is given by $\Sigma(r) = 6300\ r_{AU}^{-1}$ g/cm^2 and temperature structure by $T(r) = 1500\ r_{AU}^{-0.5}$ K, where r_{AU} is the radial distance in astronomical units (AU). This corresponds to a disk with a mass accretion rate of $5 \times 10^{-7}\ M_\odot$/year (for $\alpha = 0.002$), which is typical for young T-Tauri stars (*11*, *12*). The disk thickness ($H = c/\Omega$) increases with distance from the star as the vertical component of gravity decreases. Thus, the gas density monotonically decreases with distance around the midplane of the disk, but increases with radial distances for extended regions at higher altitudes. The pressure contours behave similarly.

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with disk evolution—indeed, their outward transport may be further encouraged by the outward flows that are present. Those materials that diffuse vertically out of this region are pushed back toward the star as outward diffusion slows and the viscous flows are directed inward.

Thus, the level to which high-temperature materials can be delivered to the cool, outer regions of a protoplanetary disk is controlled by their residence time in the "outward transport region" (OTR) around the midplane. Long residence times in the OTR can be achieved in two ways. The first is if the OTR occupies large volumes within the disk, a condition that is determined by the disk structure (Fig. 2). Disks with relatively steep surface density gradients will have larger OTRs because they have less mass in the outer disk to drive inward flows through viscous stresses. As a result, these flows are relegated to the uppermost layers of the disk where the radial volume density gradients start to become positive. This allows larger levels of outward transport (Fig. 3). Conversely, a disk with a more shallow surface density profile has a smaller OTR, resulting in less outward transport and limiting the materials in the outer disks to amorphous grains left over from the parent molecular cloud. Molecular cloud collapse calculations (*24*) predict that disks will develop surface density profiles that initially vary as $r^{-1.5}$; however, deviations from this profile arise due to nonsymmetry and magnetic-field effects, and therefore disks with a range of structures are expected. Because the largely molecular hydrogen gas in protoplanetary disks cannot be directly observed, the results here suggest that the crystallinity fraction and distribution in these disks can be used as a diagnostic of the disk structure and, when combined with other observations such as the opacity variations across the disk, may help untangle the physical properties of the disk.

Alternatively, long residence times in the OTR can be attained if materials are contained in large grains or were incorporated into larger aggregates through collisions and sticking with other grains (*25*). These larger objects would not diffuse vertically as efficiently as smaller particles (*19*), leading to higher concentrations in the OTR and larger outward fluxes (Fig. 3). If high-temperature materials were delivered in larger assemblages, these aggregates and grains would be susceptible to disruption from the energetic collisions that arise in turbulent environments (*25*). Such collisions would thus populate the outer disk with high-temperature fine-grained materials whose spectral signatures could then be observed (*9*, *10*).

That outward transport occurs most efficiently around the midplane of the disk suggests that the fraction of crystalline grains in a disk will correlate with the amount of settling that occurs, which increases as solids grow. These correlations are indeed observed because those disks that are inferred to have large crystallinity fractions based on the observed spectra are best fit by models in which the solid subdisk is flat, rather than flared (*10*). Such correlations are counter to the 1D model predictions, where an increase in particle size leads to a decrease in the outward transport efficiency because larger particles diffuse less efficiently and migrate inward more rapidly due to gas drag (*19*). Here, the outward flows within the OTR counteract the inward motions due to gas drag. These flows could also preserve the 0.1- to 1-cm CAIs in the solar nebula for the millions of years between their formation and their incorporation into meteorite parent bodies (*15*, *18*).

The variations in radial transport dynamics with height produce vertical gradients in the abundance of crystalline grains in the disk (Fig. 3). Thus, infrared observations of protoplanetary disks, which only detect radiation from the disk surfaces, will lead to underestimates of the fraction of material that was processed at high temperatures. Therefore, the reported crystallinity fractions for protoplanetary disks (*9*, *10*) should be taken as lower bounds. Such gradients are not predicted in 1D models because of the implicit assumption that all materials are well mixed with height.

This work shows that outward transport of high-temperature materials naturally occurs around the midplane of turbulent protoplanetary disks. This mode of transport would take place even if layered accretion (*26*) occurred—where the MRI generated a turbulent viscosity in the surface layers of the disk, leaving the midplane surrounded by a "Dead Zone." Hydrodynamic effects can produce turbulence even in cold,

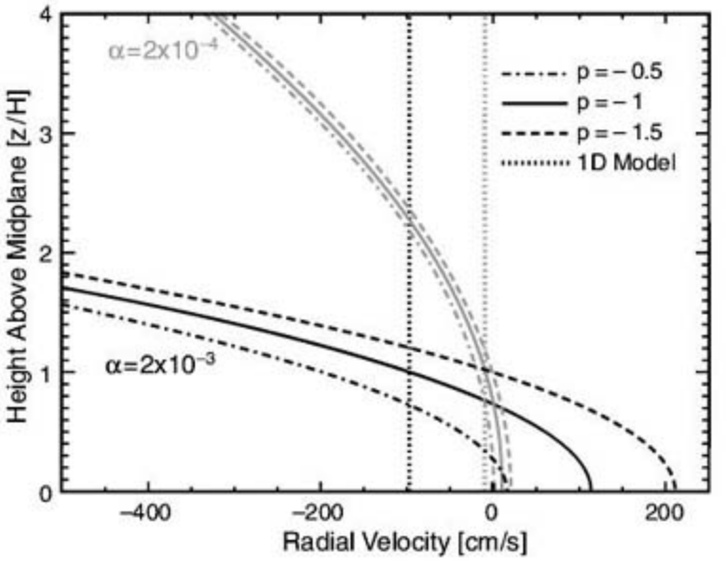

Fig. 2. The radial velocity of the gas at 1 AU in viscous accretion disks with different viscosities (values of α) and different surface density radial dependences (r_{AU}^{p}). The thermal structure is the same as in Fig. 1. The flows are determined largely by the radial gradients in gas density and temperature (*20*–*22*); thus, vertical variations in temperature would not produce substantially different results from those shown. The 1D steady-state advective velocities are shown for comparison.

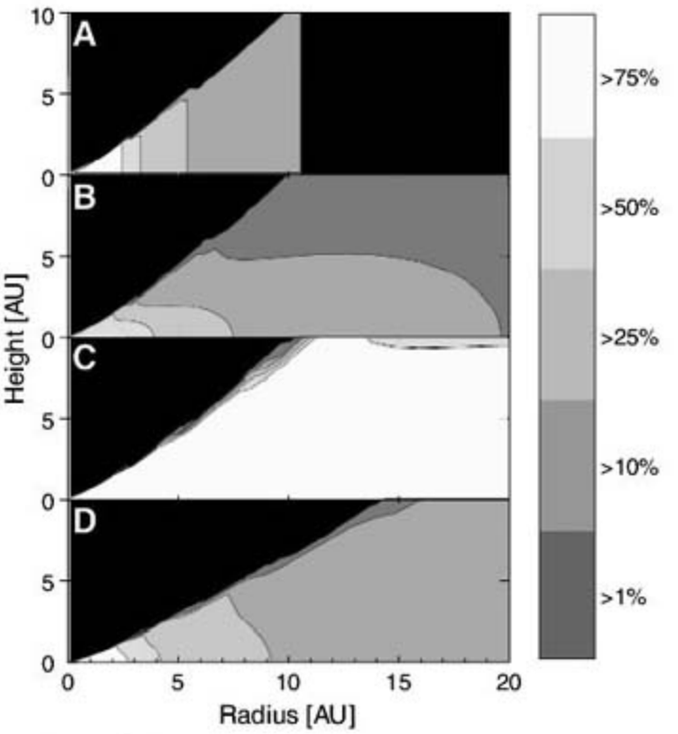

Fig. 3. Contour plots for the silicate crystallinity fraction in steady-state protoplanetary disks. In (**A**) and (**B**), the disk has the same structure and evolves as described in Fig. 1. (A) shows the results of a 1D model (*23*), whereas (B) uses the 2D model developed here. Silicates are assumed to be 1-μm spheres and initially distributed in the disk at a crystallinity fraction of 1%. Grains that are exposed to temperatures above 1100 K become crystalline, because the annealing time (<10 min) is negligible when compared to all other time scales considered (*2*, *4*). In (**C**), the disk surface density falls off as $r^{-1.5}$ with all other disk properties kept the same. In (**D**), the same disk as in (A) and (B) is used, except that solids are contained in millimeter-sized aggregates. In all cases, the vertical distribution of solids is characterized by a thickness, $H_d = [\alpha/(1 + St)]^{0.5} H$ (*19*).

neutral parts of a disk (*27*), allowing solids to diffuse outward around the midplane while still avoiding the inward flows that would frustrate their transport to the outer disk. The only requirement for this model is that the disk was hot enough to process materials at the needed temperatures. Although high mass accretion rates are initially needed to produce these temperatures, the rates that are needed to deliver large amounts of high-temperature materials to the outer disk are typical for young T-Tauri stars (*11*) and more than an order of magnitude less than required by previous models (*3*).

An important consequence of this model is that the thermally processed grains would have remained in contact with the nebular gas throughout their transport, allowing volatiles to condense on their surfaces in cooler environments. In the X-wind model (*28*), grains are processed by radiation from the Sun as they are launched above the disk in bipolar outflows. These grains would have lost their volatiles upon being heated, then decoupled from the gas to rain back onto the solar nebula. As these grains fell onto the solar nebula in the comet-formation region, there would be mixing between two components: the solar composition materials that were already present and the more refractory crystalline grains. Thus, comets that grew from these materials would be depleted in volatile elements, and those depletions would correlate with the amount of crystalline materials they contain. Preliminary analyses of the Stardust samples indicate that Comet Wild 2 exhibits no such depletions (*29*).

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A Surface-Tailored, Purely Electronic, Mott Metal-to-Insulator Transition

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Mott transitions, which are metal-insulator transitions (MITs) driven by electron-electron interactions, are usually accompanied in bulk by structural phase transitions. In the layered perovskite $Ca_{1.9}Sr_{0.1}RuO_4$, such a first-order Mott MIT occurs in the bulk at a temperature of 154 kelvin on cooling. In contrast, at the surface, an unusual inherent Mott MIT is observed at 130 kelvin, also on cooling but without a simultaneous lattice distortion. The broken translational symmetry at the surface causes a compressional stress that results in a 150% increase in the buckling of the Ca/Sr-O surface plane as compared to the bulk. The Ca/Sr ions are pulled toward the bulk, which stabilizes a phase more amenable to a Mott insulator ground state than does the bulk structure and also energetically prohibits the structural transition that accompanies the bulk MIT.

The insulating phase associated with metal-insulator transitions (MITs) (*1*–*4*) can be described as either a band insulator (such as silicon) or a Mott insulator (such as nickel oxide). A band insulator has an even number of electrons per unit cell that can be described adequately by an independent electron theory, where all of the bands are either filled or empty at 0 K. If the number of electrons in the unit cell is odd, then band theory always predicts metallicity, but when the onsite Coulomb interaction (U) is comparable in magnitude to the bandwidth (W), the material can become a Mott insulator (*1*, *2*). A transition from the Mott insulating phase to the metallic phase can be induced by temperature, pressure, magnetic field, or doping (*4*). Normally, the MIT for a band insulator is accompanied by a structural phase transition that changes or breaks the symmetry (*5*, *6*). The simplest example is a one-dimensional chain of atoms, which, as Peierls showed (*3*), is unstable because of the degeneracy caused by Fermi surface nesting at 2 k_F, where k_F is the Fermi wavevector. The lattice reconstructs itself, doubling the periodicity and lowering the electronic energy by creating a gap at the Fermi energy (E_F).

In contrast, an inherent Mott transition should be purely electronic in origin and not assisted by a structural transition (*1*, *2*, *5*). In practice, almost all of the highly correlated materials with a large enough ratio of U/W to be Mott insulators exhibit close coupling between charge, spin, and lattice, so that the Mott transition is nearly always accompanied by a structure transition. This situation complicates the understanding of the basic mechanism of a Mott MIT as a transition driven by the electron-electron (*e*-*e*) correlations. We now show that the surface layer of a Mott insulator can display a MIT independent of a structural transition.

The layered ruthenate $Ca_{2-x}Sr_xRuO_4$ shows a rich array of ground states that are associated with the intricate couplings between lattice, electron, and spin degrees of freedom (*7*–*9*). Ca^{2+} replacement of Sr^{2+} gradually enhances the rotational and tilt distortion of the RuO_6 octahedra, starting with a tetragonal *I4/mmm* structure for Sr_2RuO_4, leading to an $I4_1/acd$ structure for $Ca_{1.5}Sr_{0.5}RuO_4$, and ending with an orthorhombic *S-Pbca* structure for Ca_2RuO_4 (*9*). These structural changes lead to an evolution of the ground state, from an unconventional superconducting state in Sr_2RuO_4 (*10*) to a quantum critical point at $x = x_c \sim 0.5$ (where c is critical) and to an antiferromagnetic Mott insulating phase when $x < 0.2$ (*7*, *8*).

The layered structure of this material, which plays a key role in the anisotropic transport and magnetic properties (*7*, *8*), also makes the crystal

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amenable to creating a surface by cleaving and offers a controlled way to investigate the manifestation of broken symmetry on a Mott MIT (*11*). Bulk studies have demonstrated that the Mott transition in the low Sr-doping regime is intimately related to a structural transition (*9*). When the system changes from a metallic to a Mott insulating phase on cooling, a concomitant structural transition to a more distorted orthorhombic phase is observed in the bulk. In sharp contrast, we demonstrate here that the Mott transition on a freshly cleaved surface of $Ca_{1.9}Sr_{0.1}RuO_4$ occurs without an accompanying lattice distortion. Our observations and theoretical calculations show that the broken symmetry at the surface creates a structure that allows for an inherent, purely electronic Mott transition. Figure 1 shows unambiguous evidence for a shift of the MIT to lower temperature (T) at the surface of a $Ca_{1.9}Sr_{0.1}RuO_4$ single crystal. The bulk MIT occurs at T_c = 154 K (c, critical), as shown by the abrupt change of the bulk electrical resistivity, whereas the surface transition occurs at $T_{c,s}$ = 130 K (s, surface), as indicated by the opening of the energy gap measured by scanning tunneling spectroscopy (STS).

To investigate the surface Mott transition as well as the evolution of surface electronic properties and associated lattice dynamics, we have performed both STS and high-resolution electron energy loss spectroscopy (HREELS) measurements versus temperature on the surface of $Ca_{1.9}Sr_{0.1}RuO_4$ (*12*). Both STS and HREELS are surface-sensitive techniques: STS probes the integrated density of electronic states near E_F, and the spectra from HREELS provide the surface dielectric response through quasi-particle excitations, including phonons and low-energy electron excitations. The low-energy quasi-particle excitations near E_F, referred to as the Drude weight in energy loss spectra, provide a signature of metallicity. The information obtained from HREELS at the surface is similar to that from optical conductivity spectroscopy for the bulk.

The measured T dependence of STS and HREELS spectra shows that both the STS and HREELS spectra display no sign of an energy gap at room temperature (Fig. 2). The HREELS spectra exhibit a sizable Drude weight apparent on the right shoulder of the elastic scattering peak, indicating the metallic character of the surface. The Drude weight decreases gradually with decreasing sample temperature as the elastic peak in the HREELS spectra becomes more and more symmetric. Correspondingly, the density of states near E_F also decreases with decreasing temperature as shown in the tunneling conductance (the derivative of the tunneling current dI/dV) close to zero bias. The energy loss peak at $\hbar\omega_s \sim 81$ meV is an optical phonon associated with the apical oxygen vibration at the surface (*13*) ($\hbar$, Planck's constant; ω_s, surface phonon frequency). The corresponding bulk mode is the RuO_6-stretching A_{1g} mode (Fig. 2B, inset) that appears at a lower energy [$\hbar\omega_b \sim 72$ meV (ω_b, bulk phonon frequency)] for Ca_2RuO_4 (*14*). This surface phonon peak gradually decreases its intensity while remaining at a constant energy of ~81 meV with decreasing temperature until around 130 K.

Below 130 K, several abrupt changes occur in these spectroscopic measurements that are indicative of a distinct surface transition. An energy gap up to 0.3 ± 0.1 eV emerges in the STS spectra (Fig. 2A), indicating the establishment of an insulating state at the surface below $T_{c,s}$ = 130 K. This value of the energy gap is near that measured from the bulk of Ca_2RuO_4 (*14*–*16*). The gap of Ca_2RuO_4 obtained from the optical conductivity measurement (*14*, *15*) varies with temperature, from 0.2 ± 0.05 eV at $T_c \sim 356$ K to 0.6 ± 0.03 eV at 11 K. An analysis of the resistivity versus T gives a gap of ~0.39 eV for Ca_2RuO_4 (*16*). Simultaneously,

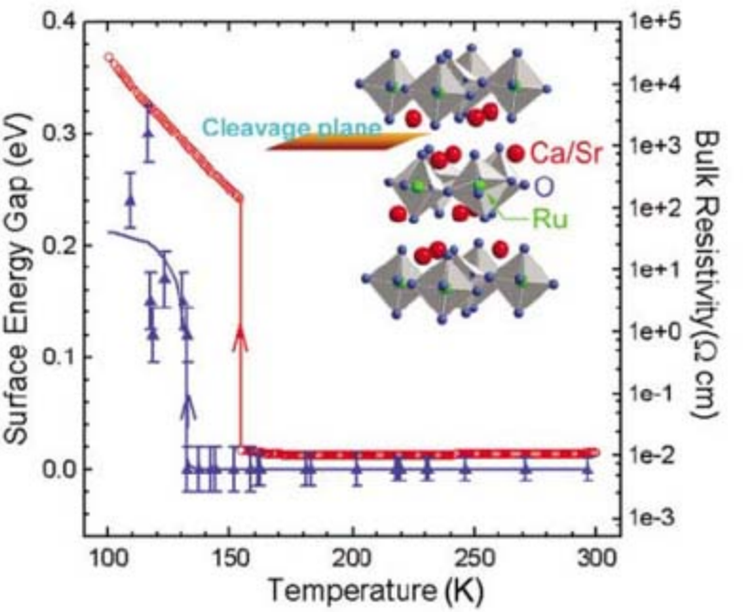

Fig. 1. Signatures of the MIT in the bulk (T_c = 154 K) and at the [001] surface ($T_{c,s}$ = 130 K) of a $Ca_{1.9}Sr_{0.1}RuO_4$ single crystal. The T dependence of the bulk resistivity (orange circles and trace) was measured using a physical property measurement system, and the surface energy gap (blue triangles and trace) was measured by a scanning tunneling spectroscope on cooling. The inset at upper right is a ball model of the unit cell of $Ca_{1.9}Sr_{0.1}RuO_4$. The surface was created by cleavage between two SrO layers without breaking RuO_6 octahedra from the same crystal used for the bulk resistivity measurement.

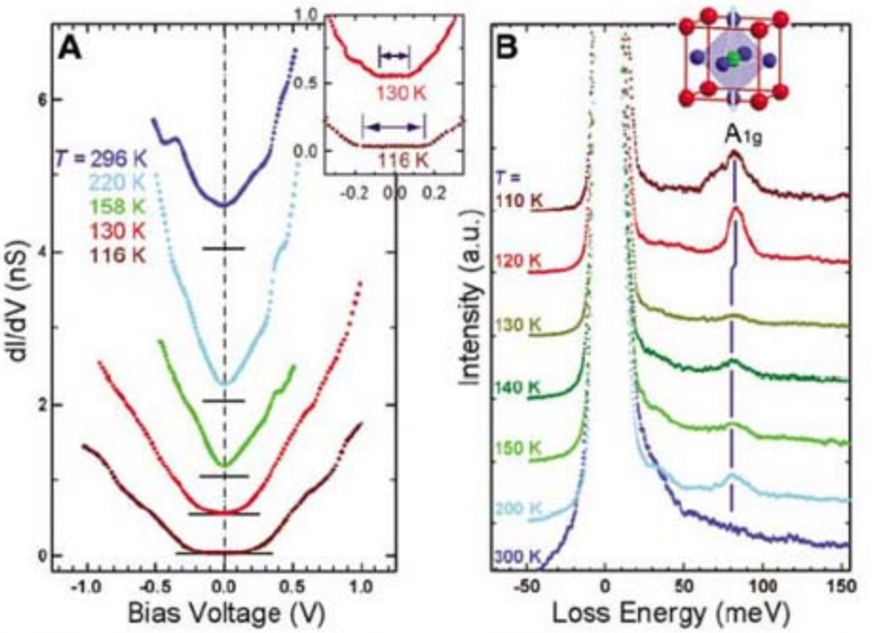

Fig. 2. **(A)** T dependence of scanning tunneling dI/dV spectra measured at the surface of $Ca_{1.9}Sr_{0.1}RuO_4$ (averaged over an area of 60 nm × 60 nm by a grid spectroscopic mode with 20 × 20 sampling pixels, sample bias V = 1.18 V, and feedback current I = 0.76 nA). The spectra are also shifted for clarity, with the zero value of dI/dV marked by solid lines. The inset is the enlargement of the spectra near E_F showing the opening energy gap (indicated by arrows) when the surface becomes insulating below 130 K. **(B)** T dependence of normalized HREELS spectra measured at the surface of $Ca_{1.9}Sr_{0.1}RuO_4$ taken with electron scattering at the specular direction. The incident electron beam energy used was 20 eV. The spectra for T < 300 K have been incrementally shifted for clarity. The marked peaks are the loss feature due to the optical phonon excitations associated with the RuO_6 stretching mode (see the schematic ball model). a.u., arbitrary units.

the stretching phonon peak shows a shift to higher energy and a sudden increase in intensity in the HREELS spectra (Fig. 2B). In addition, the linewidth of the phonon abruptly changes from ~20 meV above 130 K to 7 meV below. This change indicates a coupling between the lattice dynamics and MIT at the surface associated with a change in electron-phonon (*e-p*) interaction. But, as noted below, the change in the *e-p* coupling does not drive a structural phase transition at $T_{c,s}$.

To elucidate the correlation of these changes at the surface of $Ca_{1.9}Sr_{0.1}RuO_4$, we have analyzed the STS and HREELS spectra (*17*) to extract information about the *T* dependence of the energy gap and the Drude weight, as well as the phonon energy, intensity, and linewidth (Fig. 3) from the data taken on cooling. A sudden drop of the Drude weight and the opening of the energy gap are accompanied by an energy shift, a rapid increase in intensity, and an abrupt linewidth reduction of the surface phonon at the temperature $T_{c,s}$ = 130 K, all of which are hallmarks of a surface Mott MIT. The surface MIT temperature ($T_{c,s}$) is more than 20 K lower than T_c (154 K) in the bulk. This finding is counterintuitive, because the conventional picture suggests that *e-e* correlation effects should be stronger at the surface than in the bulk as a result of the reduced atomic coordination, thus stabilizing the Mott insulating phase and pushing the Mott transition to higher temperatures at the surface as compared to the bulk.

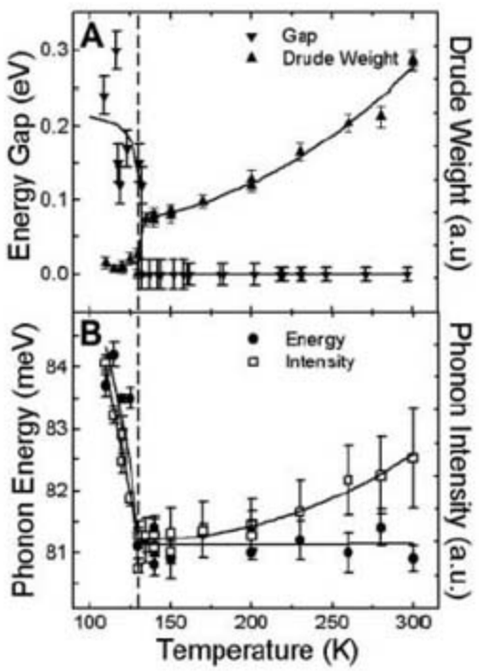

Fig. 3. Sum of the measured results for the surface MIT. **(A)** *T* dependence of the energy gap determined by the STS spectra and the Drude weight obtained from the HREELS spectra and **(B)** *T* dependence of the energy and intensity of the optical phonon measured with HREELS at the surface of $Ca_{1.9}Sr_{0.1}RuO_4$. The dashed line marks the surface MIT temperature ($T_{c,s}$ = 130 K). The solid lines are guides for the eye.

The bulk first-order Mott MIT in $Ca_{1.9}Sr_{0.1}RuO_4$ is accompanied by an abrupt lattice distortion (*9*). The bulk structure above and below the bulk MIT, as well as the difference between them, are presented in Table 1. We have determined the surface lattice structure by quantitatively analyzing the low-energy electron diffraction (LEED) *I-V* (intensity as a function of voltage) spectra (*18*) at both room temperature (RT) metallic and low-temperature (LT) insulating phases. In order to precisely determine the complex surface structure of this oxide compound, we have used a new self-consistent procedure (*19*) developed for LEED *I-V* structural determinations of oxide surfaces. The *I-V* of 16 nonequivalent beams was measured and compared with calculated intensities for surface model structures. The total *I-V* energy range (summation of energy ranges for the 16 nonequivalent beams) varied from 3982 to 4469 eV for four sets of data. A good fit with the Pendry reliability factor (*20*) R_P = 0.22 to experimental spectra was achieved, yielding the structure listed in Table 1.

A typical LEED image, which does not change with temperature from 300 to 90 K, is shown in Fig. 4A. The symmetry and the existence of a single glide line in the image pattern indicate a $p(1 \times 1)$ [001] surface of a bulk-terminated orthorhombic structure. This orthorhombic structure (with *Pbca* space group symmetry) is characterized by a static tilt and rotational distortions of RuO_6 octahedra from the simple cubic perovskite phase. However, the analysis of the LEED *I-V* data shows that surface structure remains static across both the bulk and surface MIT (Table 1) except for a very gradual thermal relaxation. The comparison of the 90 and 300 K structures reveals no measurable difference (within the error bars). The error bars associated with a change in structure can be reduced by comparing the experimental data below and above the transition. R_P for such a comparison is ~0.1, which allows us to conclude that both the octahedral tilt and the surface buckling remain unchanged within the error bars (0 ± 0.4° for tilt and 0 ± 0.02 Å for surface buckling).

Structural distortion is important to create and stabilize a Mott insulating state in the bulk of $Ca_{2-x}Sr_xRuO_4$ (*7–9*). While keeping the same symmetry, the bulk crystal undergoes a distinct structural transition at T_c that is intimately linked to the MIT (*9*). This spontaneous structural transition (Table 1) is characterized by a substantial increase in the RuO_6 tilt angle (~5°), accompanied by a reduction in the Ru–apical oxygen ion O(2) distances (~0.05 Å) and by a considerable increase of the in-plane Ru-O(1) bond lengths (~0.04 Å). Similar structural distortions were not observed on the surface; therefore, we were observing a MIT that was solely driven by *e-e* interactions. All of our structural and spectroscopic data indicate that the surface MIT is of the same nature as the bulk; that is, a Mott MIT. Thus, despite its lower transition temperature (20 K lower), the inherent Mott insulating phase at the surface may be more stable than the inherent Mott insulating phase in bulk, if the bulk structural distortion can be eliminated.

Although in the metallic phase the surface has a slightly larger RuO_6 rotation and tilt than the metallic bulk at room temperature, the observed tilts on the surface never reach the values observed in the bulk insulating phase. As shown schematically in Fig. 4B, the largest surface relaxation is the inward motion of the top Ca/Sr ions (which remains the same at both high and low temperature). This results in a static buckling in the surface Ca/Sr-O(2) layer of 0.23 Å. The explanation for this compression of the surface layer is straightforward and quite general. When the oxygen above the top Ca/Sr is removed, so is the attractive ionic force that allows the Sr to be pulled inward by the attractive forces from the oxygen below. This type of relaxation has been documented for surfaces of perovskites such as $SrTiO_3$ (*21*), $BaTiO_3$, and $PbTiO_3$ (*22*). This buckling of the surface Ca/Sr-O layer impedes the structural transition that occurs in the bulk at T_c.

Table 1. Comparison between the bulk and [001] surface lattice distortion of $Ca_{1.9}Sr_{0.1}RuO_4$ in orthorhombic structure, mainly the rotational angle (ϕ), tilt angle (θ), and changes of volume of the octahedra. Errors are given in parentheses, with the error bars for the surface measurements determined using R_P (*20*). The Δ_b(LT-RT) and Δ_s(LT-RT) columns are the comparisons of the experimental data between the LT insulating and RT (300 K) metallic phase of the bulk and surface, respectively. Δ_z is the difference in the vertical position between Ca/Sr and the O(2) ions in the surface Ca/Sr-O(2) plane.

	Bulk (*9*)			Surface	
T (K)	300	10	Δ_b(LT-RT)	90	Δ_s(LT-RT)
Ca/Sr-O(2) Δ_z (Å)	0.159(0.002)	0.179(0.002)	−0.020(0.003)	0.23(0.03)	0.00(0.04)
θ: O(1) (degrees)	6.5(0.1)	11.16(0.05)	4.64(0.05)	9.0(0.7)	0.1(1.1)
θ: O(2) (degrees)	5.2(0.1)	9.40(0.07)	4.1(0.7)	6.8(0.5)	0.3(0.9)
Ru-O(1) (Å)	1.939(0.002)	1.987(0.002)	−0.048(0.002)	1.97(0.02)	0.01(0.04)
	1.948(0.002)	1.988(0.002)	−0.040(0.002)	1.98(0.02)	0.01(0.04)
Ru-O(2) (Å)	2.040(0.001)	1.991(0.001)	0.049(0.001)	2.05(0.01)	0.01(0.02)
ϕ (degrees)	12.65(0.06)	11.77(0.05)	−0.88(0.08)	16(2)	0(3)
Volume RuO_6 (Å^3)	10.27	10.48	0.21	10.64	−0.02

The above scenario is confirmed by our first-principles calculations using a plane-wave pseudopotential method and local density approximation [see (*23*, *24*) for technique details]. We calculate the total energy as a function of structural distortions, namely RuO_6 rotation and tilting, while fixing the lattice parameters to the experimental ones (neutron diffraction data for the bulk (*9*) and the LEED results for the surface shown in Table 1). With the bulk structural parameters, our theoretical calculations reproduce the two stable bulk lattice structures (Fig. 4C): one with a tilt angle of ~6.5° for the metallic phase and the other with a tilt angle of ~10° for the insulating phase. To simulate the situation of the surface, we include the enhanced buckling of the Ca/Sr-O plane in a bulk calculation. As shown in Fig. 4C, this enhanced buckling pins the tilt angle at ~7°, making the increased tilt energetically unfavorable and inhibiting the structural transition. The calculated tilt angle (~7°) is in excellent agreement with LEED *I-V*–determined results, even though this is not a surface calculation. Although our calculations do not directly account for the broken symmetry of the surface, the search for total energy minima using a bulk calculation including the observed surface structural distortions reveals the influence of the surface enhanced buckling on the ground state structure.

With no structural transition involved in the surface Mott MIT, we can ask what drives the observed inherent Mott MIT at the surface of $Ca_{1.9}Sr_{0.1}RuO_4$. In $Ca_{2-x}Sr_xRuO_4$, three t_{2g} orbitals ($4d_{xy}$, $4d_{yz}$, and $4d_{zx}$) contribute to the electronic states near E_F. In the bulk crystal, both tilt and flattening of the RuO_6 octahedra favor an antiferromagnetic ground state, whereas both tilt and rotational distortion stabilize the insulating phase by narrowing the t_{2g} bandwidth (*23*, *24*). Although never reaching the bulk insulating phase values (~10° on average), the surface tilt angle (~8° on average) is slightly greater than the bulk metallic phase values (~6° on average). In addition, the surface RuO_6 rotational distortion is greater than that in the bulk. All of these factors, plus the reduced coordination at the surface (*25*–*27*), which presumably enhances surface correlations, point in the direction of increasing the ratio of correlation to bandwidth (U/W). It is this enhanced ratio that is strong enough to drive the surface Mott MIT without the necessity of a structural transition.

A recent finite-temperature (250 K) multiband dynamical mean field theory calculation for the Mott MIT in $Ca_{2-x}Sr_xRuO_4$ (*28*) presents a model that lets us test these assertions. The occupancy of the in-plane d_{xy} band (n_{xy}) is critical for creating the Mott insulating state. We have used density functional theory (DFT) to calculate n_{xy} for the three relevant structures: (i) the RT bulk (RTB) metallic phase, (ii) the LT bulk (LTB) insulating phase, and (iii) the surface (s), with n_{xy}(s) calculated for a bulk with this structure. The DFT calculation yields n_{xy}(RTB) = 0.71, n_{xy}(LTB) = 0.75, and n_{xy}(s) = 0.73. The n_{xy} value for the pure Sr compound is 0.64. This calculation clearly shows the tendency, without any correlation of the three different structures, toward Mott insulator formation. The surface is more susceptible to an inherent Mott MIT than the room-temperature bulk.

The identification of the appropriate microscopic order parameter for a finite temperature MIT has and continues to be actively discussed (*29*–*31*). The order parameter associated with an inherent Mott MIT is masked by complications arising from coupled transitions (*31*). Figure 3 shows that, for the surface inherent Mott MIT, there are several experimental observables that can be configured as order parameters. The normalized gap seen with STS is an appropriate order parameter, as is the gap seen in optical conductivity measurements (*29*, *30*). The Drude weight can be configured to be another order parameter and, because of the strong *e-p* interaction, the energy and intensity of the optical phonon offer two other physical observables that can be defined appropriately to serve as order parameters. The data in Fig. 3 show how these observables all give the same $T_{c,s}$. Comparison to the first-order structural transition that occurs in the bulk at the MIT temperature indicates that the surface transition may be more gradual. Whether the surface Mott MIT is a second-order phase transition awaits a much more detailed investigation. What is required is a detailed study of the thermal hysteresis of the STS energy gap. However, the bulk first-order character of the Ca-rich single crystals in the $Ca_{2-x}Sr_xRuO_4$ family complicates these measurements. Further experiments are also needed to elucidate the nature of the surface transition. A decisive experiment would be an angle-resolved photoemission study of the evolution of the coherent quasi-particle band as T approaches $T_{c,s}$, especially for $T < T_c$.

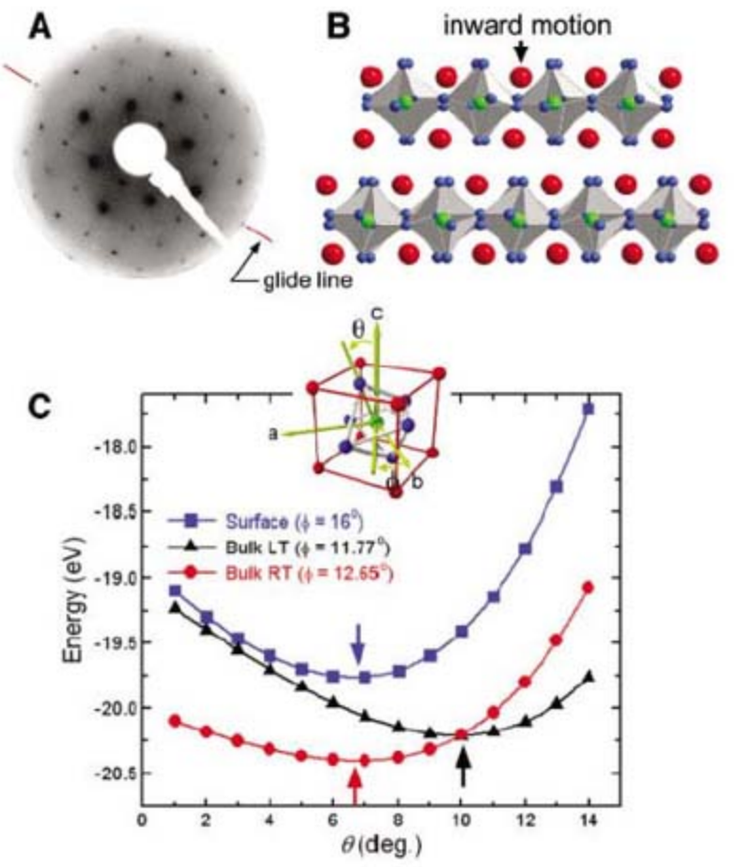

Fig. 4. (A) A typical LEED image at the cleaved surfaces of $Ca_{1.9}Sr_{0.1}RuO_4$ at RT, taken with an electron beam energy of 170 eV. The tilt distortion of RuO_6 octahedra is evident by the existence of only one glide line (on which fraction spots are extinct) instead of two perpendicular glide lines due to the broken symmetry. **(B)** A ball-model side view of the determined structure from the surface (top layer) to the bulk (bottom layer) of $Ca_{1.9}Sr_{0.1}RuO_4$. The distinct inward motion of Ca/Sr ions at the surface is indicated by the arrow. **(C)** The calculated total energy versus RuO_6 tilt angle (θ) for three different lattice structures: the bulk RT structure (red symbols), the bulk LT structure (black symbols), and the surface structure (blue symbols). For each case, the calculations were nonmagnetic and were done starting with a bulk structure with the experimentally determined lattice parameters and the rotational angles (ϕ). The inset at top schematically defines the rotation and tilt distortion of RuO_6 octahedron. The arrows indicate the calculated tilt angles (θ) with the minimum energies corresponding to the three structures.

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12. High-quality $Ca_{1.9}Sr_{0.1}RuO_4$ single crystals for this study were grown with the use of an optical floating zone furnace, and their bulk properties were in good agreement with reported values (*7*, *8*). The bulk resistivity

was measured with a physical property measurement system. The electrical resistivity shows the MIT at T_c = 154 K on cooling (Fig. 1) and exhibits large thermal hysteresis behavior indicating a first-order character of the MIT. $Ca_{1.9}Sr_{0.1}RuO_4$ crystals for scanning tunneling microscopy (STM), LEED, and HREELS measurements were mounted on the sample plates with conducting silver epoxy, and a small metal post was glued on top. The crystal was cleaved by knocking off the post in ultrahigh vacuum with a base pressure of 1.0×10^{-10} torr, producing a flat shiny [001] surface that yielded a sharp LEED pattern. The STM images of the freshly cleaved surfaces show large micrometer-sized terraces. Both the LEED pattern and atomically resolved STM images indicate that the surface has a well-ordered lattice structure. All surface steps are integral multiples of ~6.4 Å, which is the spacing between two nearest-neighbor RuO_6 octahedron layers (Fig. 1). LEED *I-V* analysis shows that the surface is composed of Ca/Sr-O terminations.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5850/615/DC1
Materials and Methods
Figs. S1 to S4
References

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A Synthetic Lectin Analog for Biomimetic Disaccharide Recognition

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Carbohydrate recognition is biologically important but intrinsically challenging, for both nature and host-guest chemists. Saccharides are complex, subtly variable, and camouflaged by hydroxyl groups that hinder discrimination between substrate and water. We have developed a rational strategy for the biomimetic recognition of carbohydrates with all-equatorial stereochemistry (β-glucose, analogs, and homologs) and have now applied it to disaccharides such as cellobiose. Our synthetic receptor showed good affinities, not unlike those of some lectins (carbohydrate-binding proteins). Binding was demonstrated by nuclear magnetic resonance, induced circular dichroism, fluorescence spectroscopy, and calorimetry, all methods giving self-consistent results. Selectivity for the target substrates was exceptional; minor changes to disaccharide structure (for instance, cellobiose to lactose) caused almost complete suppression of complex formation.

Carbohydrates are challenging substrates for host-guest chemistry (*1*–*4*). They possess extended, complex structures that require large receptor frameworks for full encapsulation. The differences between them are often subtle (e.g., the stereochemistry of a single hydroxyl group), so that meaningful selectivity is hard to achieve. Most particularly they are found in water and, with their arrays of hydroxyl groups, they quite strongly resemble water. The first task of a receptor is to discriminate between solvent and substrate, and in the case of carbohydrates this is clearly nontrivial. There is evidence that even nature finds the problem difficult. Though critical for many biological processes (*5*–*7*), protein/carbohydrate binding is remarkably weak (*8*). For example, lectins, the most common class of natural receptors, quite often show affinities [association constants (K_a)] of less than 10^4 M^{-1} (*9*). Previous work on synthetic receptors points in the same direction. Biomimetic (*10*, *11*) carbohydrate receptors have been sought to model natural recognition and also for applications such as glucose sensing. However, whereas good systems are available for organic solvents (*1*–*3*, *12*–*15*), there has been very limited success in water (*1*–*4*, *16*, *17*).

We have targeted carbohydrates with all-equatorial arrays of polar substituents, such as β-glucose **1** (Fig. 1). These substrates have axially directed CH groups, forming small apolar patches at top and bottom. Accordingly, our hosts incorporate roof and floor motifs composed of aromatic hydrocarbons, capable of hydrophobic attraction reinforced by CH–π interactions. These aromatic regions are supported by pillars containing polar groups that can hydrogen bond to the substrate –OH groups (Fig. 1). In prototypes of formula **2**, the roof and floor are provided by biphenyl units, and the pillars are isophthalamides. Recently, we prepared a water-soluble (*18*–*20*) variant of **2** and tested its ability to bind carbohydrates in aqueous solution (*21*). The system was successful but not spectacular. Glucose was bound measurably but weakly (K_a = 9 M^{-1}) and with moderate selectivity (e.g., glucose:galactose = ~5:1). Though encouraging, these properties are hardly comparable to those of lectins.

In biology, most carbohydrate recognition involves oligosaccharides, so we were interested to learn if these extended substrates could be addressed by our strategy (*22*–*26*). We therefore considered larger versions of our receptor, aimed at all-equatorial disaccharides such as cellobiose **4** (Fig. 1). We now report the design, synthesis, and study of tetracyclic disaccharide receptor **3**. This host achieves a dramatic leap in performance, showing good affinities and outstanding selectivities for its chosen substrate. It comes remarkably close to true biomimicry and provides a realistic synthetic model for protein/carbohydrate recognition.

Receptor **3** is constructed from two building blocks. A *meta*-terphenyl structure provides the roof and floor, defining the length of the cavity, and isophthalamide units serve as pillars. Each pillar includes two amide linkages, with the potential to hydrogen bond to the –OH groups in **4**. The pillars are also furnished with externally directed tricarboxylate units, to promote solubility and resist aggregation in water. An important consideration was the possibility of cavity collapse, allowing the aromatic surfaces to meet. In aqueous solution, such a process should be strongly favored, driven by hydrophobic interactions. To counter this tendency, the design incorporated five of the rigid isophthalamides, spaced fairly evenly around the terphenyl units. Molecular modeling (*27*, *28*) confirmed that collapsed structures were strongly disfavored; all conformations found within 20 kJ mol^{-1} of the baseline possessed substantial cavities.

The receptor was synthesized from benzenoid precursors via Suzuki-Miyaura couplings and macrolactamizations (*29*). As expected, it dissolved freely in water to give well-resolved ^{1}H nuclear magnetic resonance (NMR) spectra, implying a monomeric species (fig. S4). Initial complexation studies were performed using ^{1}H NMR titrations with cellobiose **4** as a substrate.

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The spectra show clear indications of binding (Fig. 2A). Sequential disaccharide additions caused decay of the receptor spectrum and growth of a new set of signals. These changes are consistent with complex formation, in which exchange between bound and unbound forms is slow on the NMR time scale. As the titration proceeds, signals due to the receptor are replaced by those of the complex. The spectrum of **3** is relatively simple, reflecting its symmetry; although there are 33 aromatic protons, there are only 11 distinct environments. However, once the disaccharide is bound, all of these environments become different. Accordingly, the spectrum of the complex contains many more peaks.

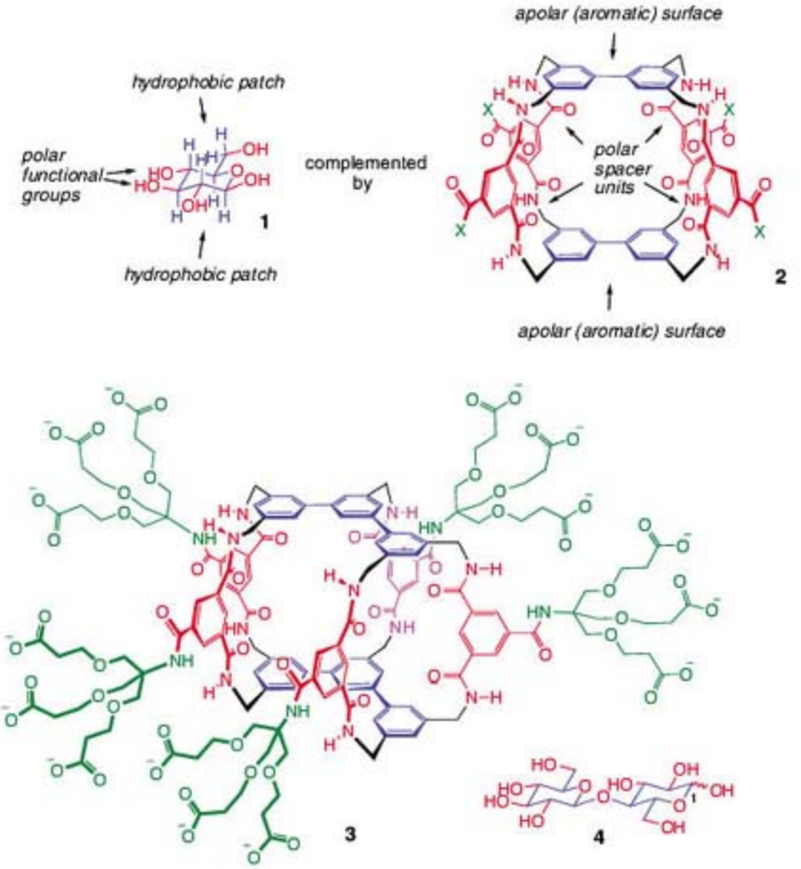

Fig. 1. The design of receptors for all-equatorial carbohydrates. (**Top**) β-D-Glucose **1** and complementary receptor framework **2**. Polar and hydrophobic moieties are shown in red and blue, respectively. X can be varied to control solubility. Versions of **2** are described in (*19*–*21*). (**Bottom**) Disaccharide receptor **3**, reported herein, and cellobiose **4**, an intended substrate. The roof and floor of **3** are provided by *meta*-terphenyl units (blue). There are five isophthalamide pillars, two at either end (red) and one located centrally (magenta). The water-solubilizing tricarboxylate units are shown in green. The molecule has two planes of symmetry, one lying parallel to and between the terphenyls, and the other passing through the central (magenta) isophthalamide.

The affinity of **3** for cellobiose was estimated by integration of an NMR signal from the complex against that of an internal standard (*29*). Errors were significant because of signal overlap, but an approximate value of ~600 M^{-1} could be obtained (figs. S5 and S6). To improve accuracy, binding was also investigated by induced circular dichroism (ICD) and fluorescence spectroscopy (*29*). The addition of cellobiose to **3** in water gave a clear ICD signal (Fig. 2B) and also a 370% increase in fluorescence output (Fig. 2C). Titration data from both methods gave excellent fits to a 1:1 binding model, with K_a values of 570 M^{-1} and 560 M^{-1}, respectively (Fig. 2D and fig. S14). For final confirmation, isothermal titration calorimetry was also applied. The fit to a 1:1 model was again good, with K_a = 650 M^{-1}, change in enthalpy ΔH = –3.22 kcal mol^{-1}, and $T\Delta S$ = 0.62 kcal mol^{-1} (where T is temperature and ΔS is the change in entropy) (fig. S15). Complex formation is mainly enthalpically driven and therefore not dominated by the classical (entropy-driven) hydrophobic effect (*30*). The balance between enthalpy and entropy lies comfortably within the range observed for lectins (*9*), supporting a lectin-like binding mode involving both hydrogen bonding and apolar interactions (*31*).

NMR studies yielded quite detailed structural information about the complex. Two-dimensional

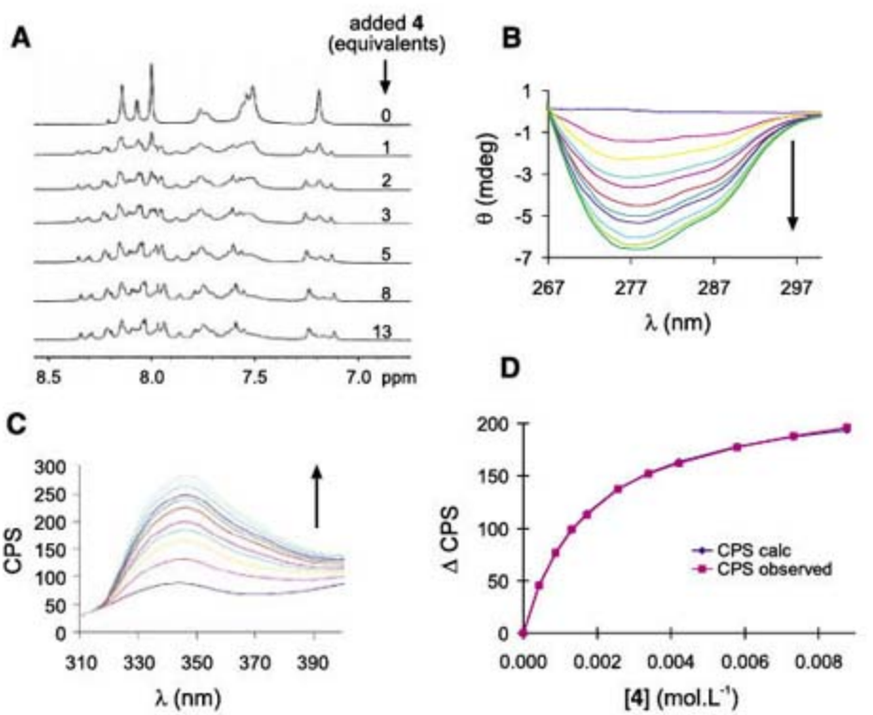

Fig. 2. Evidence for complex formation between receptor **3** and cellobiose **4**. (**A**) Partial ^{1}H NMR spectra from the addition of **4** to **3** in D_2O. The signals shown are due to receptor aromatic protons. The concentration of **3** = 0.5 mM. (**B**) ICD caused by the addition of **4** (0 to 7 mM) to **3** (0.25 mM). λ, wavelength. (**C**) Increase in fluorescence output caused by the addition of **4** (0 to 9 mM) to **3** (0.01 mM). CPS, counts per second. (**D**) Analysis of data from (C) by nonlinear least-squares curve fitting, assuming 1:1 binding stoichiometry. K_a = 560 M^{-1}, limiting ΔCPS = 320 CPS. Observed and calculated points are almost coincident.

Table 1. Binding constants of carbohydrates to **3** in aqueous solution, as measured by ^{1}H NMR, ICD, and fluorescence titrations. Aqueous solution is defined as D_2O for the NMR measurements and H_2O for CD and fluorescence. T = 298 K, except where indicated. ND indicates not done. For structural formulas of **5** to **16**, see Fig. 4.

Carbohydrate	K_a (M^{-1})		
	^{1}H NMR	ICD	Fluorescence
D-Cellobiose (**4**, 1β–OH:1α–OH = 3:2)	600*§	580	560
Methyl β-D-cellobioside (**5**)	‡	910	850
D-Xylobiose (**6**)	‡	250	270
D-*N*,*N*′-diacetylchitobiose (**7**)	120*	ND	120
D-Lactose (**8**)	‡	11	14
D-Mannobiose (**9**)	‡	13	9
D-Maltose (**10**)	‡	15	11
D-Gentiobiose (**11**)	ND	12	5
D-Trehalose (**12**)	‖	‖	ND
D-Sucrose (**13**)	ND	‖	‖
D-Glucose (**14**)	11†§	12	‖
D-Ribose (**15**)	ND	‖	‖
D-*N*-acetylglucosamine (**16**)	24†	ND	19

*Slow exchange on the NMR time scale. †Fast exchange on the NMR time scale. ‡Intermediate exchange (leading to broad peaks and preventing the determination of K_a). §T = 278 K. ‖No change in spectrum upon addition of carbohydrate.

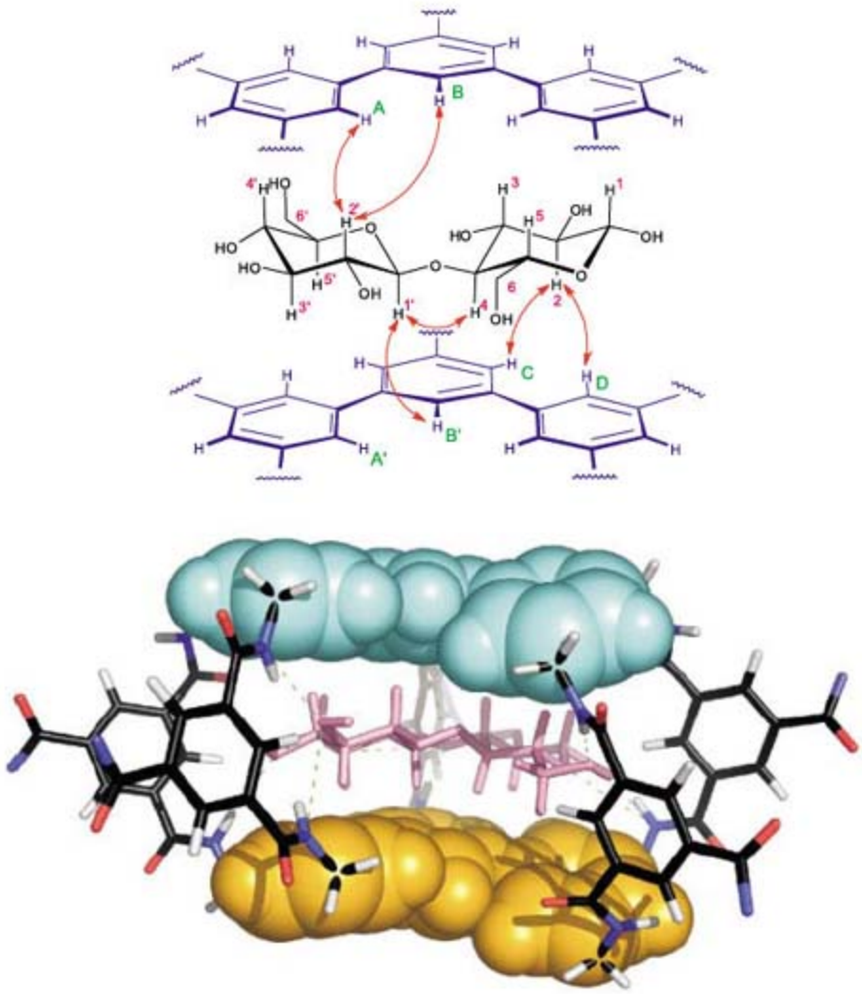

Fig. 3. (Top) NOESY contacts observed for the complex between β-cellobiose and receptor **3**. **(Bottom)** A computational model of the complex, consistent with the NOE data. Water-solubilizing side chains are omitted for clarity. The cellobiose is colored pink, and the terphenyl units are shown in space-filling mode. Polar interactions are represented as dotted lines. Black, carbon; red, oxygen; blue, nitrogen; and white, hydrogen.

rotating-frame nuclear Overhauser effect spectroscopy (ROESY) shows chemical-exchange cross peaks linking bound and unbound cellobiose chemical shifts, so that the shifts for the bound carbohydrate could be determined (figs. S7 to S9). Cellobiose in solution consists of a 2:3 mixture of α and β anomers (**4α** and **4β**), with the C1–OH group in the axial and equatorial orientations, respectively. For **4β**, a full set of cross peaks was observed, and a complete assignment was therefore possible (table S1). All the carbohydrate protons moved upfield upon binding, by amounts between 0.5 and 2.1 parts per million. Such changes are consistent with the expected structure, in which the disaccharide is sandwiched between the aromatic surfaces.

Results from nuclear Overhauser effect spectroscopy (NOESY) further support this mode of binding. A strong cross peak between the cellobiose 1′ and 4 protons established that the glycosidic linkage was in the syn conformation (*32*), giving the required flat profile (Fig. 3). Intermolecular cross peaks were observed between aromatic receptor signals and all carbohydrate chemical shifts (fig. S10). The involvement of protons from both faces of the disaccharide provides clear proof of encapsulation. The aromatic region of the spectrum was too crowded for a comprehensive analysis but a few contacts could be identified unambiguously (Fig. 3). Strong NOE signals of similar intensities were observed between H2′ and two protons in the crescent of the terphenyl (A and B in Fig. 3). A similar pair of contacts were detected between H2 and two exterior terphenyl protons (C and D in Fig. 3). A further strong NOE was found between H3′ and the terphenyl HA′, and a weaker signal was observed between H1′ and HB′. The 2′–A/B contacts were used as constraints for molecular modeling, in which a Monte Carlo molecular mechanics search was performed with both distances held at 2.5 Å, and then the resulting conformations were reminimized with no constraints (*27*, *28*). The baseline structure is shown in Fig. 3. It retains the 2′–A/B contacts (2.63 and 2.87 Å) while independently predicting the 2–C/D contacts (2.58 and 2.78 Å), the 3′–A′ proximity (3.04 Å), and the longer 1′–B′ distance (3.44 Å). The structure features 8 intermolecular hydrogen bonds and ~10 CH–π interactions and seems a persuasive model for the complex. The chiral guest imparts a twist to the host, consistent with the observed ICD.

The NMR spectra were also examined for evidence of binding to **4α**. Again, the ROESY spectra showed cross peaks between bound and unbound carbohydrate, allowing for the assignment of most disaccharide protons (table S2). However, NOESY spectra suggest that the binding was weaker. If so, the affinity for **4β** must be greater than the measured value of ~600 M^{-1}, considering that this figure is an average for the two anomers.

To assess its selectivity, receptor **3** was tested against 10 disaccharides and 3 monosaccharides

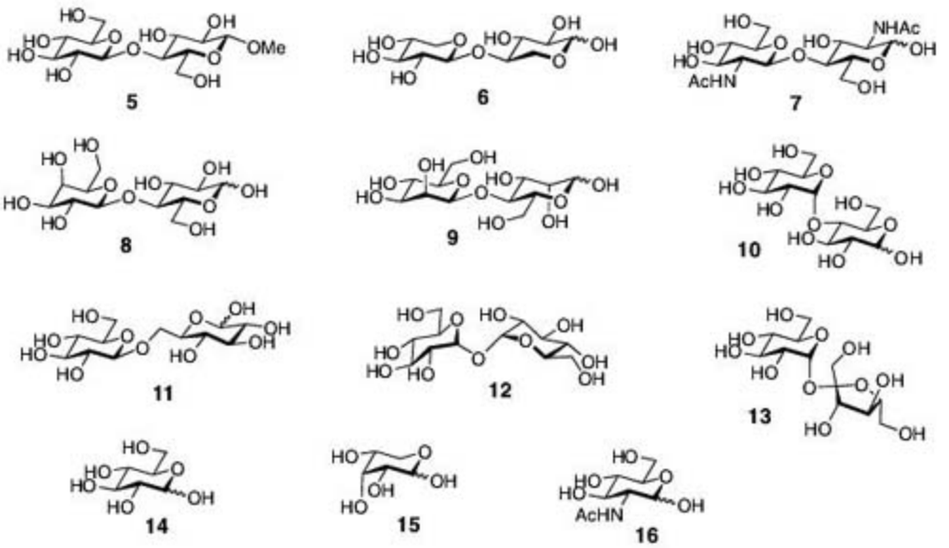

Fig. 4. Carbohydrate substrates used with receptor **3** (in addition to cellobiose **4**). For binding results, see Table 1. Me, methyl; Ac, acetyl.

(Fig. 4 and Table 1) (*29*). At least two techniques were applied in each case (*33*). Agreement between the methods was generally good. Methyl β-D-cellobioside **5** might be seen as a model for **4β** and was bound with $K_a \sim 900\ M^{-1}$. Two closely related all-equatorial disaccharides, xylobiose **6** and *N*,*N*′-diacetylchitobiose **7**, were complexed somewhat less strongly ($K_a = 260$ and $120\ M^{-1}$, respectively). Of the remaining substrates, the highest value was $\sim 20\ M^{-1}$ (for *N*-acetylglucosamine **16**). Most remarkable were the results for lactose **8** and gentiobiose **11**. The former possesses just one axial OH group, the latter an all-equatorial structure that is slightly longer than **4**. In both cases, the change from **4** was enough to reduce the binding constant to $\sim 12\ M^{-1}$. Indeed, the selectivity for **4** versus nontargeted disaccharides was generally ~50:1 or better.

The ^{1}H NMR measurements also provided information about binding kinetics. Whereas binding to **4** and **7** was slow on the NMR time scale, exchange of the other substrates was intermediate or fast (Table 1). This behavior lies within the range for lectins, which can show fast or slow exchange by NMR (*34*, *35*). The differing exchange rates were exploited in a competition experiment that confirmed the receptor's selectivity for cellobiose **4**. The addition of eight nontarget substrates (**8** and **10** to **16**; 20 mM each) to **3** caused broadening and shifting of the receptor ^{1}H NMR signals, as is expected for intermediate or fast exchange (fig. S52). However, upon further addition of only 9 mM **4**, these signals were replaced almost quantitatively by the spectrum of complex **3**·**4**. The cellobiose complex was thus formed nearly exclusively in the presence of an 18-fold excess of nontarget carbohydrate. The experiment shows that, like a natural lectin, receptor **3** can bind its target from a complex mixture of potential substrates.

In terms of affinity, receptor **3** cannot match the highest values found in nature (*36*). However, the K_a value for β-cellobiosyl (approaching $10^3\ M^{-1}$) is comparable to that for many carbohydrate/protein interactions (*9*). Moreover, the specificity of **3** for a narrow class of substrates is high, even by biological standards. This performance is achieved with a system that is far smaller than a typical lectin. The sense of selectivity accords with the design, which was specifically aimed at all-equatorial disaccharides. The targets **4**, **6**, and **7** relate to important biopolymers. Cellobiose **4** is the repeat unit of cellulose, the most abundant organic material on earth and a major renewable resource. Xylobiose **6** and *N*,*N*′-diacetylchitobiose **7** are representative of xylan and chitin, the most abundant polysaccharides after cellulose. Both are important resources, and chitin is a potential target for insecticides and antifungal agents (*37*). Further work may lead to molecules that can bind the polymers themselves, with potential for applications in processing (e.g., solubilization) and biomedical research.

Synthetic lectins could also be immobilized and used to separate carbohydrates or glycoconjugates, or they could be fitted with transducing elements (such as fluorophores) to give specific saccharide sensors. In the shorter term, receptor **3** provides a realistic model for carbohydrate-binding proteins. Affinities, selectivities, thermodynamic parameters, and kinetic properties all lie within the spread of values observed for lectins. At the same time, the receptor possesses a robust, covalently enforced binding cavity. This should allow studies under conditions that would denature proteins, adding an important tool for exploring the principles underlying biological carbohydrate recognition.

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38. This work was supported by European Commission Research Training Network contract HPRN-CT-2002-00190 and Engineering and Physical Sciences Research Council grant EP/D060192/1. A.P.D. dedicates this paper to the memory of Peter Davis.

Supporting Online Material

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Upper Mantle Discontinuity Topography from Thermal and Chemical Heterogeneity

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Using high-resolution stacks of precursors to the seismic phase *SS*, we investigated seismic discontinuities associated with mineralogical phase changes approximately 410 and 660 kilometers (km) deep within Earth beneath South America and the surrounding oceans. Detailed maps of phase boundary topography revealed deep 410- and 660-km discontinuities in the down-dip direction of subduction, inconsistent with purely isochemical olivine phase transformation in response to lowered temperatures. Mechanisms invoking chemical heterogeneity within the mantle transition zone were explored to explain this feature. In some regions, multiple reflections from the discontinuities were detected, consistent with partial melt near 410-km depth and/or additional phase changes near 660-km depth. Thus, the origin of upper mantle heterogeneity has both chemical and thermal contributions and is associated with deeply rooted tectonic processes.

Globally imaged upper mantle seismic discontinuities (*1*) observed at depths near 410, 520, and 660 km arise from mineralogic phase transformations of the mineral olivine to wadsleyite, wadsleyite to ringwoodite, and ringwoodite to perovskite + magnesiowüstite, respectively (*2*) (Fig. 1A). For simplicity, we refer to each discontinuity by an average depth, for example, "410 km" and "660 km," although the exact depth of each boundary varies. The region between 410 km and 660 km is known as the mantle transition zone (MTZ). The slope of the phase transition boundary in pressure-temperature space, that is, the Clapeyron slope, is positive for the olivine-to-wadsleyite transition (*3*), resulting in a shallower 410-km discontinuity in cold regions and a deeper 410 km in hot areas. The ringwoodite-to-perovskite phase transition has a negative Clapeyron slope (*4*); therefore, the 660 km is deeper in cold areas and shallower in hot regions. Consequently, 410- and 660-km depth perturbations are opposite and anticorrelated for thermal anomalies extending across the MTZ, which has been used in past studies to infer mantle temperature [e.g., (*5*–*8*)].

We investigated upper mantle structure beneath South America and the surrounding oceans, a region with prolonged subduction of the Nazca plate along the western coast of South America, mid-ocean spreading centers at the mid-Atlantic ridge and along the East Pacific Rise, and several volcanic hotspots. Seismic investigations of MTZ thickness and discontinuity structure beneath South America have used precursors to the *SS* seismic phase (Fig. 1A), receiver functions (*9*), and near-source reflected and converted waves (*10*, *11*). Past *SS* analyses of this region were global studies (*5*–*7*) reliant on long-period (>25 s) and comparatively sparse data, retrieving long-wavelength structure (typically greater than 2000- to 3000-km lateral scales); receiver function and converted wave analyses provide higher-resolution information but are localized to areas beneath seismographic stations. Where resolved, these studies identified a relatively thick MTZ beneath South American subduction, consistent with the expected presence of a cold slab.

We extended our *SS* precursor method (*12*) to shorter period energy (~10 s) with an order of magnitude more data that past efforts, using broadband data from global earthquake sources (Fig. 1B). Our final data set consists of more than 16,000 high-quality broadband seismograms that densely sample our study region (Fig. 1C). *SS* precursor amplitudes are typically 1 to 10% of the main *SS* amplitude; thus, stacking is necessary to bring precursors out of the background noise (Fig. 1A); we stacked data in 1000-km-radius geographic bins. We exclude epicentral distance windows exhibiting interference between precursors and other seismic phases that can skew predicted discontinuity depths (figs. S1 and S2). Before stacking, corrections for mantle heterogeneity, varying crustal thickness, and surface topography are applied (*13*).

A bootstrap resample (n = 300) (*14*) of seismograms within each bin is used to evaluate whether the 410-km (*S410S*) and 660-km (*S660S*) precursor stacks amplitudes are above the 95% confidence interval. For each bin, a frequency histogram of bootstrap-predicted precursor depths is constructed from the arrival time of the maximum-stacked amplitude within a ±15 s window around the predicted precursor arrival time in each bootstrap resample. Stacks containing coherent precursory energy display amplitudes well above the 95% confidence interval; at long periods (25 s), calculated discontinuity depth bootstrap histograms display clear single peaks, with the most frequent histogram value nearly identical to the peak precursor energy arrival time from a stack of all data (Fig. 2). However, at shorter periods (10 s), the bootstrap-derived discontinuity depth distributions sometimes reveal a bimodal distribution, implying multiple reflectors. We use such histograms for inferring single versus multiple reflections near the phase boundaries.

Discontinuity depth histograms for bins near specific tectonic features indicate an MTZ generally thickened beneath subduction and slightly thinned beneath mantle hotspots (figs. S3 and S4). The 410-km discontinuity is unexpectedly deep by up to 10 to 15 km just east of the subducting Nazca slab beneath the north and central portion of the South American continent (Fig. 3); this is the opposite of what is expected for a cold MTZ associated with long-lived subduction. The 660-km discontinuity beneath

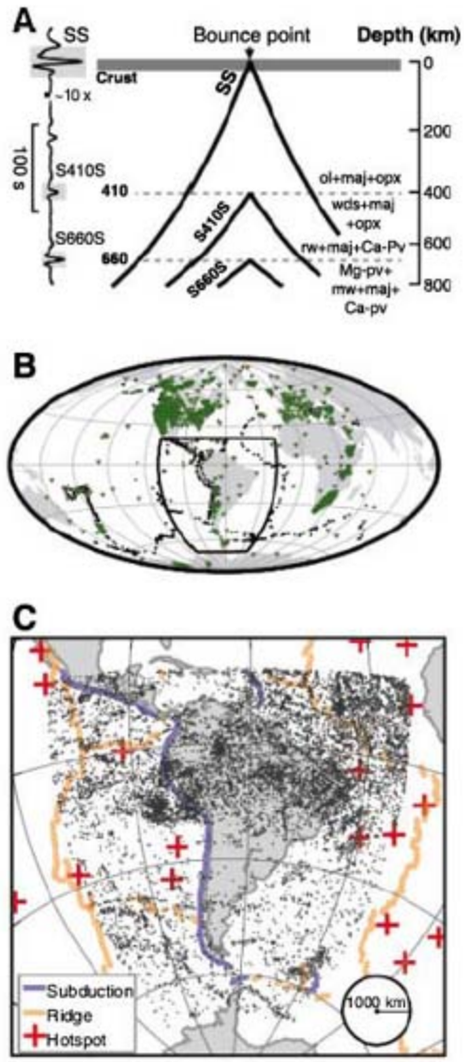

Fig. 1. (**A**) Schematic cross-section of *SS*, *S410S*, and *S660S* upper mantle ray paths halfway between earthquake and receiver with dominant MTZ mineralogy: olivine (ol), orthopyroxene (opx), majorite (maj), wadsleyite (wds), ringwoodite (rw), Ca-perovskite (Ca-pv), magnesiowüstite (mw), Mg-perovskite (Mg-pv). A synthetic waveform is shown on the left. (**B**) The distribution of earthquakes (black points) and seismic stations (green triangles) used in our study region (outlined box). (**C**) The location of *SS* bounce points (black dots) and major tectonic features (*30*) and hotspots (*31*). A 1000-km-radius bin is shown for scale.

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subduction and the South American continent is deepened by 15 to 30 km, consistent with cold material intersecting this boundary. The thickened MTZ (fig. S4) is due to a greater offset of the 660-km discontinuity than for the 410 km. These features are independent of the tomography models used to correct travel times before stacking (fig. S3) and are visible in past studies of this region (*5*, *9*), although those studies focused on MTZ thickness.

In addition to the depressed 410 km to the east of subduction, multiple reflectors on both the 410- and 660-km discontinuities are evident for the 10-s period stacks. This behavior occurs at the intersection of the slab and the 410-km boundary, as indicated by the bimodal distribution in the histogram depths: a shallow reflector at 395- to 400-km depth and a deeper reflector at 410 to 415 km. In several cross-sections, an elevated 410 km from the west overlaps a depressed 410 km to the east. A stepped 410-km discontinuity also appears beneath ridges or hotspots in several cross-sections. Additionally, on the Pacific Ocean side, the 660 km appears as two reflectors, one at 640- to 645-km depth and another at 665- to 670-km depth, up to 3000 km away from the slab. Multiple discontinuities are only apparent with short period data (Fig. 2); these high-resolution shear velocity features have not been previously detected using *SS* precursors. However, some studies of *PP* precursors (*15*), near-source reflected *P* waves (*16*), and receiver function studies (*17*) have noted multiple discontinuities in the vicinity of the major phase boundaries.

The depressed 410-km discontinuity east of a cold subducting Nazca plate cannot be solely explained by a thermal origin. If present, metastable olivine within the slab may depress the 410-km boundary (*18*); however, this effect is confined to within the slab (e.g., 50 to 100 km laterally, not thousands of kilometers). Compositional heterogeneities transported by the sinking slab can perturb phase transition stability, depth, and sharpness (*19*).

Subduction may carry an appreciable amount of H_2O into the MTZ, either within the slab or by viscous entrainment of hydrated mantle wedge material (*20*). Experiments suggest that wadsleyite and ringwoodite are hydrophilic relative to olivine and capable of holding up to several weight percent (wt %) H_2O (*21*, *22*). Increasing H_2O reduces the olivine-to-wadsleyite phase transition depth and deepens that of ringwoodite to perovskite + magnesiowüstite. Thus, elevated hydration thickens the MTZ while reducing MTZ seismic velocity and density (*20*). Hydrated wadsleyite is chemically buoyant compared with its anhydrous counterpart (*22*) and should remain at the top of the MTZ, potentially melting (*23*). Hydrated wadsleyite can seismically mask the 410-km phase boundary if the H_2O concentration is ≥0.75 wt % (fig. S16); the transition from hydrated upper MTZ to less hydrated lower MTZ can produce a seismic impedance contrast consistent with experimental predictions and with our observations. A hydrated "lens" of wadsleyite at the top of the MTZ (Fig. 4 and figs. S16 to S18) can thus appear as a deepened 410-km discontinuity. The large east-west lateral extent of the buoyant hydrated wadsleyite lens is consistent with trench rollback migrating the input of hydrated materials westward. Seismic reflections from the base of the lens should weaken with either decreased H_2O content (as expected to the east away from the slab) or broadening of the wet-to-dry wadsleyite transition. We observe decreased *S410S* amplitudes from the large-scale depressed 410-km boundary (fig. S17).

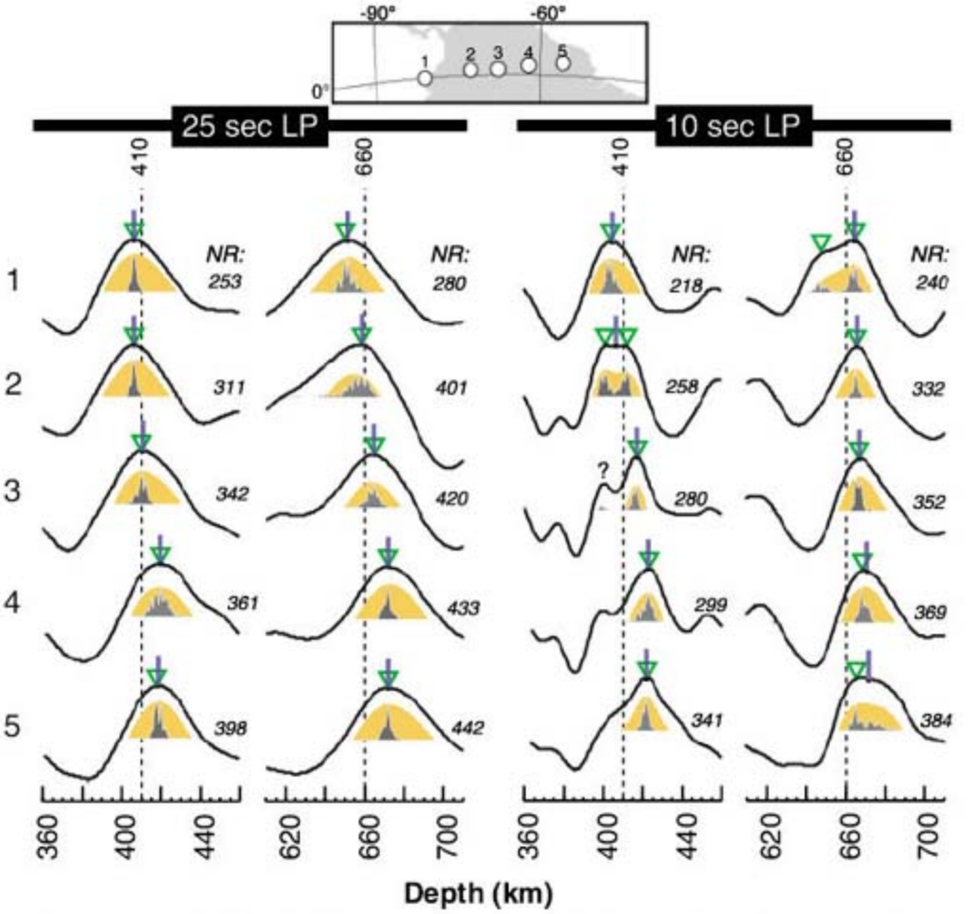

Fig. 2. Histogram stacks for *S410S* and *S660S* precursors in five example bins (inset map). Data are low-pass filtered at 25 s (left) and 10 s (right). NR is the number of records in each stack. Stacked traces (solid black lines) are underlain by energy falling above the bootstrap 95% confidence interval (orange) and a histogram of the peak bootstrap amplitudes (gray). Discontinuity depths are picked for the peak amplitude of the stacked trace (blue lines) and the mode(s) of the bootstrap resample (green triangles).

Other possibilities can produce topography on the 410-km discontinuity. For example, experimental work on Mg_2SiO_4-Fe_2SiO_4 at high pressures and temperatures finds that enriching Mg relative to Fe increases the pressure of the olivine to wadsleyite phase transition [e.g., (*24*)]. Increasing the Mg content of $(Mg,Fe)_2SiO_4$ from the expected 89% Mg to 92% Mg results in a 7- to 10-km deeper 410-km discontinuity. This is not unexpected, because melting in the overlying mantle wedge preferentially extracts Fe, leaving a magnesium-enriched residue that should be viscously entrained and brought into the MTZ. If trench rollback migrates the input of entrained wedge residue westward, a compositionally varying 410-km discontinuity trough may result (fig. S18D). Both interpretations depend on mantle wedge chemistry, degree of viscous coupling, and the detailed history of trench rollback, which are not precisely known.

The long-wavelength depression on the 660-km discontinuity beneath South America (Fig. 3 and figs. S5 to S15) is consistent with either a remnant thermal anomaly from the previous slab location or past stalling and/or accumulation of slab material at the 660-km discontinuity that has since subducted into the lower mantle. A deepened 410-km discontinuity overlying a wide 660-km discontinuity depression has been similarly observed to the west of Japan (*25*, *26*).

The 660-km discontinuity is elevated 5 to 10 km directly beneath the East Pacific Rise and the Mid-Atlantic Ridge (Fig. 3, profiles A-A′, B-B′, and C-C′). There is evidence for multiple reflections from the 410-km in these regions, consistent with a melt layer in warmer mantle enriched in CO_2 or H_2O (*27*, *28*). It is widely agreed that seismic velocity reductions beneath mid-ocean ridges is confined to the upper few hundred km of the mantle, although a thinned MTZ beneath ridges underlain by an elevated

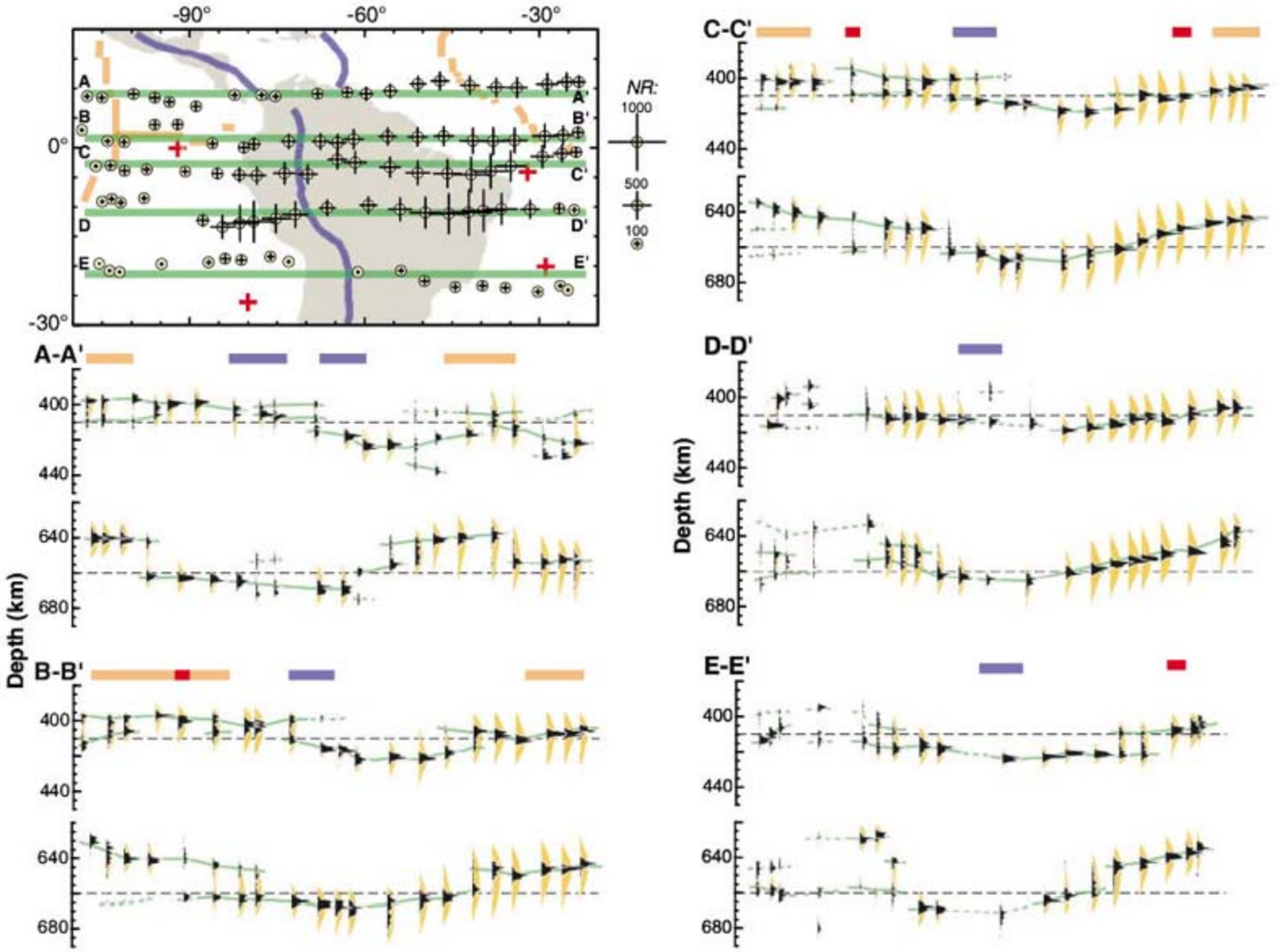

Fig. 3. East-west cross-sections of discontinuity topography and map giving cross-sections (green lines), bin locations (white circles), average record number (black crosses), and surface features (Fig. 1C legend). Discontinuity-depth histograms are plotted (as in Fig. 2) for each bin. Interpreted structure is drawn in green and dotted where less uncertain. Horizontal color bars denote locations of ridges (orange), the estimated location of slabs in the MTZ (blue), and hot spots (red) that intersect cross-sections (see also additional cross-sections in figs. S5 to S15).

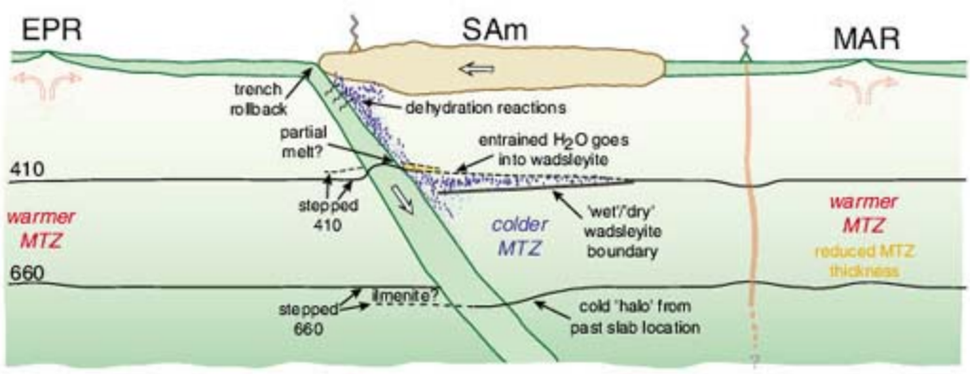

Fig. 4. An H_2O-rich lens underplating the 410-km discontinuity in cross-section view, relative to the East Pacific Rise (EPR), South American continent (SAm) and Mid-Atlantic Ridge (MAR). Trench migration contributes to the hydrated wadsleyite lens evolution, the base of which is detected in our study. The multiplicity of reflectors near 410- and 660-km depths may be explained by partial melt at the 410-km boundary and by the presence of akimotoite below the 660-km discontinuity.

660-km boundary suggests that some MTZ material, at least locally, is warmer than the surroundings.

The origin of double discontinuities near the slab may in part be due to lateral smearing of a step offset in the phase boundary on either side of the slab (i.e., aliasing of structure). Alternatively, H_2O content should be highest at the slab, which may give rise to a localized melt layer atop the 410-km boundary (*16*), with a reflective interface at the top and bottom of the melt layer. The double discontinuity sometimes present near 660-km depth may result from the ringwoodite to Mg-perovskite + magnesiowüstite transition underlain by a weaker discontinuity from the ilmenite (akimotoite) to perovskite transformation, which multi-anvil experiments (*29*) suggest should occur in colder regions. The detection of multiple discontinuities supports the presence of chemical heterogeneity within the mantle and underscores the importance of phase changes in minerals outside the olivine system.

High-resolution mapping of MTZ discontinuities using broadband data reveal a deepened 410-km near subduction, an up-warped 660-km beneath ridges, and multiple reflectors near 410- and 660-km depth. These observations highlight both chemical and thermal heterogeneities in

Earth's upper mantle related to large-scale convective processes.

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The Impact of Agricultural Soil Erosion on the Global Carbon Cycle

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Agricultural soil erosion is thought to perturb the global carbon cycle, but estimates of its effect range from a source of 1 petagram per year^{-1} to a sink of the same magnitude. By using caesium-137 and carbon inventory measurements from a large-scale survey, we found consistent evidence for an erosion-induced sink of atmospheric carbon equivalent to approximately 26% of the carbon transported by erosion. Based on this relationship, we estimated a global carbon sink of 0.12 (range 0.06 to 0.27) petagrams of carbon per year^{-1} resulting from erosion in the world's agricultural landscapes. Our analysis directly challenges the view that agricultural erosion represents an important source or sink for atmospheric CO_2.

Humans have drastically altered the global carbon cycle, mostly through increased use of fossil fuels and land use change (*1*). Global earth system models (*2*, *3*) represent well the changes in carbon flux between soil and atmosphere resulting from the reduced carbon inputs to soil and the accelerated decomposition of soil organic carbon (SOC) that accompany conversion of land from an undisturbed state to agricultural use (*4*, *5*). In contrast, the carbon dynamics of the well-documented acceleration of soil erosion and deposition (and resultant lateral fluxes of SOC) associated with conversion of land to agricultural use are poorly understood (*6*).

Soil erosion removes SOC from the site of formation and results in its burial in depositional environments. Recent analyses have identified three key mechanisms whereby these geomorphic processes, together or separately, may result in a change in the net flux of carbon between the soil and atmosphere (fig. S1). Mechanism M1 involves replacement of SOC at eroding sites as a result of continued inputs from plants and decrease in SOC available for decomposition (*6*, *7*); mechanism M2 is the deep burial of allochthonous and autochthonous carbon (*8*) and inhibited decomposition upon burial (*6*, *9*, *10*); and mechanism M3 is the enhanced decomposition of SOC as a result of the chemical or physical breakdown of soil during detachment and transport (*11*). The fundamental controls on the magnitude of the erosion-induced sink or source are then the rate at which SOC is replaced at sites of erosion, changes in the reactivity of SOC as a result of transport and burial, and the rates of soil erosion and deposition. Previous global assessments of the influence of erosion and deposition on carbon dynamics have made markedly different assumptions about these controls, resulting in the diametrically opposed assertions of a global net release or source of 0.37 to 1 Pg C year^{-1} (*12*, *13*) versus a net uptake or sink of 0.56 to 1 Pg C year^{-1} (*6*, *9*, *10*) as a consequence of erosion on agricultural lands.

The controversy about the role of erosion in the global carbon cycle reflects the inherent difficulty of quantifying a net flux controlled by interacting processes that are most often studied in isolation. We examined the integrated effect of the interacting processes using evidence for (i) the rate of SOC replacement at sites of erosion, (ii) the fate of the eroded and buried SOC within agricultural watersheds, and (iii) global soil erosion and soil carbon erosion rates (*14*). The first two lines of evidence were derived from a comprehensive large-scale survey of the SOC and caesium-137 (^{137}Cs) inventories (mass per unit area to given depth) of agricultural soils in Europe and the United States (table S1) that allows us to assess quantitatively the relationships between lateral and vertical SOC fluxes. We examined 1400 soil profiles from 10 watersheds (1 to 14 ha), including noneroded soils and eroding hill slopes as well as colluvial soils where sediment and SOC are buried. The artificial fallout radioisotope

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Table 1. Watershed-averaged sediment and SOC budgets derived from the model simulations for the intermediate scenario. The rates are representative of the whole period of agricultural activities.

Site	Area (%)		Lateral sediment transfers (Mg ha^{-1} year^{-1})		Lateral SOC transfers* (g C m^{-2} year^{-1})		Vertical carbon transfers† (g C m^{-2} year^{-1})		Ratio vertical/lateral carbon flux‡ (%)		
	Ero	Depo	Ero	Depo	Ero	Export	Ero	Depo	Min	Mean	Max
1	45	20	22.7	16.5	13.2	3.6	2.5	0.0	17	19	24
2	45	21	14.7	7.8	12.8	6.0	5.7	1.4	43	45	55
3	44	26	12.8	11.4	16.6	1.9	5.2	2.3	28	31	53
4	33	20	15.2	9.2	10.6	4.2	3.2	−1.1	27	30	42
5	47	35	13.4	11.3	10.1	1.6	2.4	−0.8	14	24	42
6	42	21	13.1	9.0	21.0	6.7	5.2	−0.7	11	25	39
7	39	22	6.4	3.5	6.2	2.8	1.6	−0.8	16	26	44
8	20	14	5.3	5.0	3.2	0.2	0.7	0.1	16	21	30
9	49	33	15.4	n.a.	32.2	n.a.	5.7	n.a.	11	18	22
10	47	34	13.4	n.a.	29.7	n.a.	5.7	n.a.	12	19	24
Average	41	25	13.2	9.2	15.5	3.4	3.8	0.05	19	26	38
Std	(±9)	(±7)	(±5)	(±4)	(±10)	(±2)	(±2)	(±1)	(±10)	(±8)	(±12)

*SOC erosion calculated as *Cw. Ecs* / 100, where *Cw* is the carbon content (%) for the top layer and *Ecs* is the erosion rate (g m^{-2} year^{-1}), both averaged over the watershed. SOC export is calculated as *Cw. (Ecs-Dcs)* / 100, where *Dcs* is the deposition rate. †Positive values indicate a net flux to soils; negative values indicate a net flux to the atmosphere. ‡Ratio is calculated using the lateral and vertical fluxes from the eroding sites. The values are derived from a conservative (Min), intermediate (Mean) and extreme (Max) model scenario (*14*).

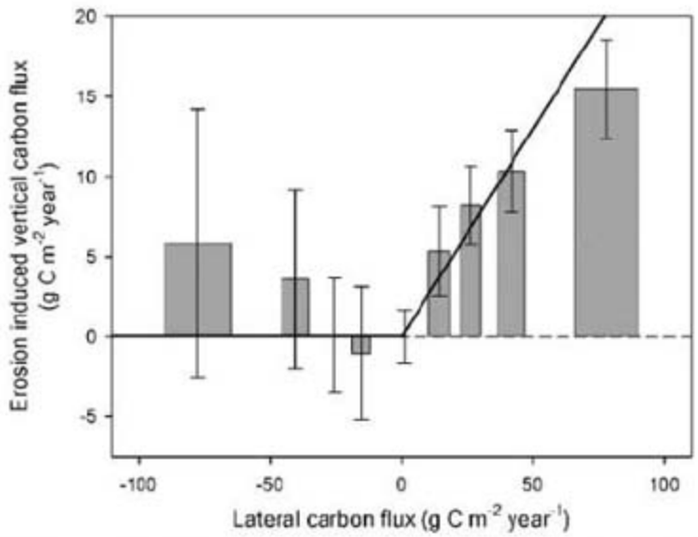

Fig. 1. Erosion-induced vertical carbon exchange between soils and atmosphere derived from 1400 profile measurements, grouped by lateral SOC fluxes (i.e., SOC erosion rates; positive values indicate erosion, negative deposition). SOC erosion is derived from the simulated SOC content (%) for the topsoil averaged over the watershed and profile-specific erosion rate derived from the ^{137}Cs data. Positive vertical exchange indicates a net flux to soils (sink); negative values indicate a flux to the atmosphere (source). The values are derived from the intermediate model scenario (*14*). The ranges of carbon erosion rates are −10 to 10, 10 to 20, 20 to 35, 35 to 50, and >50. Bar heights indicate mean values; error bars indicate 95% confidence intervals. Bars are centered on their median carbon erosion rate, and the width is proportional to their SD. The solid line represents the watershed-averaged relation (i.e., 26% and 0% replacement for the eroding and depositional areas, respectively; see Table 1).

^{137}Cs was used as a tracer for soil material to determine rates of lateral soil transfer and the corresponding rates of subsoil excavation and soil burial relative to uneroded sites. The net vertical (soil-to-atmosphere) carbon flux associated with erosion and deposition was derived by establishing the difference between measured SOC inventories and SOC inventories simulated to result from lateral redistribution of SOC while assuming no net exchange of carbon between soil and atmosphere (*15*). The third line of evidence is provided by revised estimates of the contemporary global lateral fluxes of sediment and SOC in agricultural landscapes as a result of water and tillage erosion (the effect of wind erosion is not addressed). These estimates were derived using spatially explicit models of soil erosion in conjunction with global databases of land use, soil, climate, and SOC.

Mean rates of soil loss from the eroded areas in the 10 watersheds that we examined ranged from 4 to 23 Mg ha^{-1} year^{-1}. These high rates of soil erosion were associated with rates of SOC export from the eroded areas that ranged from 3 to 32 g C m^{-2} year^{-1} (Table 1). The SOC budgets of all watersheds derived here (Table 1) are consistent with the operation of mechanism M1, in which the eroded areas of all 10 watersheds are found to act as sinks of atmospheric carbon, with a range of uptake from 1 to 6 g C m^{-2} year^{-1}. This behavior is consistent with results of simulation studies (*16*–*18*) and with field data on the age of carbon and the presence of new carbon in eroding soil profiles (*7*). Despite large variability in climate, soils, and agricultural management, there is a correlation between sink strength and rates of SOC erosion found in the data for the 647 profiles subject to net erosion (Fig. 1). The average vertical:lateral flux ratio (carbon sink:SOC erosion ratio) is 0.26 (±0.08), whether derived using point data (Fig. 1) or integrated watershed data (Table 1, range of 0.11 to 0.55). The consistency of this proportion suggests that it can be used with predictions of lateral carbon fluxes (carbon erosion) to derive reliable estimates of sink strength under a wide range of climatic and management regimes. In deriving this proportion, we have taken into account site to site variations in the amount of subsoil SOC incorporated into surface horizons by erosion and variations in the SOC inventories. Furthermore, because only a fraction of the carbon exported from the eroded areas since the start of cultivation has been replaced by additional carbon derived from the atmosphere, the SOC inventories of eroding profiles have been subject to progressive depletion. The proportion of eroded SOC that is replaced is similar to the magnitude of the active SOC pool, which turns over within years to decades, and it seems probable that this pool undergoes most rapid replacement (*19*). The more passive pools accumulate as a result of a slow cascade of transformations, and both a longer period of time and a larger total throughput of SOC are required to replace these.

Although replacement of exported carbon at sites of erosion provides a sink of atmospheric carbon, the net effect of erosion and deposition on carbon exchange with the atmosphere is dependent on the fate of the SOC exported from the eroded areas. In the 10 sites examined here,

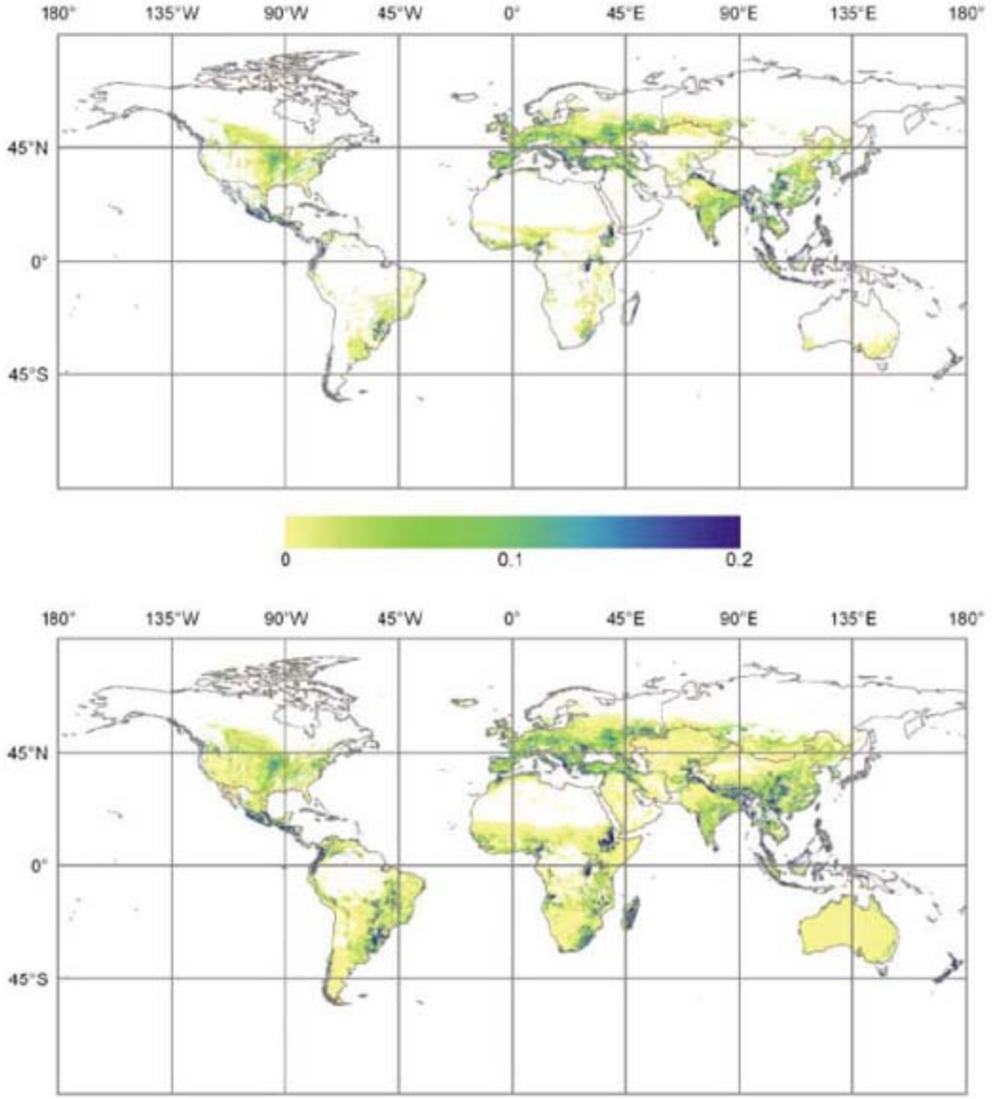

Fig. 2. (Top) Simulated global distribution of cropland SOC erosion by water and tillage. **(Bottom)** Simulated global distribution of agricultural carbon erosion (cropland + pasture- and rangeland) (Mg C ha^{-1} $year^{-1}$).

53 to 95% of eroded carbon was conserved and found to be redeposited within the watersheds over an area covering 14 to 35% of the watershed. This is consistent with earlier reports of the large amounts of retained erosion in watersheds (*20*).

In contrast to the areas of net erosion, the 256 profiles subjected to deposition show variation from a net source to a net sink (Fig. 1), with a watershed-averaged mean of 0 ± 1 g C m^{-2} $year^{-1}$ (Table 1). These data suggest that preservation of buried carbon (mechanism M2) is effective and that, at the sites investigated, losses associated with transport (mechanism M3) are relatively minor. It appears that SOC redeposited within a short distance of the site of erosion, as in the sites examined here, is retained. Therefore, at the scale of the watershed/zero-order basin in which erosion and deposition occurs, the net exchange with the atmosphere is a sink, the magnitude of which is determined by the replacement of carbon at eroded locations with no measurable offset or additional contribution from the proximal depositional areas (*6*). The composite magnitude of the sinks derived at this scale also sets the upper limit for the larger (landscape/regional) scale sink. However, it must be recognized that the fate of any SOC exported into the fluvial network and transported to distal depositional environments will determine the extent to which the landscape/regional scale sink magnitude approaches this upper limit (*21*).

On the basis of this analysis, the two most important controls on sink magnitude are identified as the rate at which SOC is eroded and the proportion of eroded SOC that is replaced at the sites of erosion. The last has been constrained by the analysis above. Using the models described in the (*14*), we estimate that the global contemporary agricultural sediment flux on cropland is about 22 Pg $year^{-1}$ and that an additional approximately 11 Pg $year^{-1}$ is mobilized on pasture- and rangelands (table S2). These sediment flux estimates correspond with a cropland SOC erosion rate of 0.32 Pg C $year^{-1}$ and a total agricultural SOC erosion rate of 0.47 to 0.61 Pg C $year^{-1}$ (Fig. 2). When the rate of SOC replacement on eroded soils and the reduced decomposition in depositional environments found here are applied to the world's agricultural soils, the erosion-induced sink strength is ~0.12 Pg C $year^{-1}$ (range 0.06 to 0.27) (*22*), of which 67% is accounted for by croplands.

The analysis presented here corroborates the hypothesis of an erosion-induced sink (*6*). However, our estimate is smaller than other estimates, which range between 0.56 and 1.2 Pg C $year^{-1}$ (*6*, *9*, *10*). The reasons for this difference are twofold. First, global erosion rates have been overestimated in some studies because of a reliance either on aerial extrapolation of a limited number of plot experiments that are strongly biased toward steep slopes and fallow conditions (*23*) or on very coarse-grid implementation of hill slope erosion models (*24*, *25*). Our approach, which explicitly accounts for watershed-scale processes at a very fine spatial resolution, yields erosion rates that reflect that most agriculture is situated on lowlands with relatively low relief intensities and consequently low erosion rates (*26*). Second, previous estimates were largely based on analysis of SOC stabilization in depositional environments and implicitly assumed that SOC contents were at steady state at eroded areas (i.e., 100% replacement of eroded SOC) (*9*, *10*). We suggest that dynamic replacement of eroding carbon (*6*) is limited to the active carbon pools, which constitute on the order of 25% rather than 100% of the eroded carbon, and that this limits the magnitude of the atmospheric sink. Even the relatively modest sink that we derive may overestimate the true sink, because we have not accounted for decomposition losses from the exported SOC (*21*) and because the 26% replacement that we used is based on data from high-input agricultural systems, which may be less sensitive to yield decline than are low-input systems (*27*, *28*).

Our analysis shows that vast quantities of sediment and SOC (0.47 to 0.61 Pg C $year^{-1}$) move laterally over Earth's surface as a result of agricultural erosion. The erosion conveyor excavates subsoil at eroding locations, transports it downslope through surface horizons, and buries former top-layer soil in depositional areas. Hence, both the spatial and vertical profile distribution of SOC in agricultural landscapes is continuously evolving, and carbon stock assessments based on topsoil sampling only is likely to result in erroneous interpretations and conclusions. Inclusion of tillage erosion, which is generally not included in studies of lateral SOC fluxes (*16*), substantially increased the flux as well as the area over which these processes take place. Our results indicate that over the past 50 years, globally, ~16 to 21 Pg C (*29*) have been buried within agricultural landscapes. However, the long-term stability of these pools under present and future climate disturbance remains highly uncertain (*8*, *30*). The next steps in the quantification of the role of lateral SOC fluxes in the global carbon budget will require consideration for the potential increase in decomposition rates at sites of deposition as a

result of global warming, desiccation, land use change (*31*), and re-excavation by increased rates of water erosion (*24*), as well as the dynamics of SOC replacement at sites of erosion. Based on our analysis, we reject both the notion that agricultural erosion substantially offsets fossil fuel emissions and the view that agricultural erosion is an important source of CO_2.

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19. The proportion of eroded carbon being replaced at the eroding sites ranges from 0.11 to 0.55 when all errors are accounted for (Table 1). Based on radiocarbon studies of density separates (*32*) and bulk fractions (*33*) and on mass weights of SOC fractions (*34*) for globally diverse soils that are not generally eroded, the fraction of SOC that turns over within years to decades varies from 15 to 80%. Eroding sites are less studied, and carbon dynamics may be affected by the introduction of exposed subsoil, which is enriched with less reactive carbon substrates but may also provide nutrients for enhanced plant growth.
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22. We compared our global results with our high-resolution simulations at various spatial scales and established that our approach provides unbiased and scale-independent estimates of SOC erosion at the continental scale. The range is derived by using the 95% lower/upper confidence level of the replacement term (13 to 45%) using the conservative/extreme model scenario in combination with a low/high global SOC erosion estimate.
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26. There is also indirect evidence that previous estimates of agricultural erosion are much too high. Estimates using data on river sediment load (*36*) estimated that human activities have led to an increase of ~2 Pg in the global river sediment flux to the ocean (if effects of large dams are omitted). Typical sediment delivery ratios for large basins is on the order of 10% (*11*), that is, an increase in global river sediment flux by 2 Pg should correspond to a global agricultural erosion rate on the order of 20 Pg, which is much more consistent with our estimates.
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37. We thank R. Buddenmeier, S. Billings, A. Nicholas, W. Van Muysen, A. Berhe, and H. Van Hemelrijck for help and advice during the course of this work. Much of this work was supported by the European Commission under the Marie Curie IntraEuropean Fellowship Programme. The contents of this work reflect only the authors' views and not the views of the European Commission. K. Van Oost holds a postdoctoral position at the Fund for Scientific Research Flanders (FWO). J. Six and S. De Gryze were supported by the Kearney Foundation of Soil Science.

Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5850/626/DC1
Materials and Methods
SOM Text
Figs. S1 to S5
Tables S1 to S3
References

29 May 2007; accepted 13 September 2007
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Why Is Climate Sensitivity So Unpredictable?

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Uncertainties in projections of future climate change have not lessened substantially in past decades. Both models and observations yield broad probability distributions for long-term increases in global mean temperature expected from the doubling of atmospheric carbon dioxide, with small but finite probabilities of very large increases. We show that the shape of these probability distributions is an inevitable and general consequence of the nature of the climate system, and we derive a simple analytic form for the shape that fits recent published distributions very well. We show that the breadth of the distribution and, in particular, the probability of large temperature increases are relatively insensitive to decreases in uncertainties associated with the underlying climate processes.

The envelope of uncertainty in climate projections has not narrowed appreciably over the past 30 years, despite tremendous increases in computing power, in observations, and in the number of scientists studying the problem (*1*). This suggests that efforts to reduce uncertainty in climate projections have been impeded either by fundamental gaps in our understanding of the climate system or by some feature (which itself might be well understood) of the system's underlying nature. The resolution of this dilemma has important implications for climate research and policy.

We investigate a standard metric of climate change: Climate sensitivity is defined as the equilibrium change in global and annual mean surface air temperature, ΔT, due to an increment in downward radiative flux, ΔR_f, that would result from sustained doubling of atmospheric CO_2 over its preindustrial value ($2 \times CO_2$). It is a particularly relevant metric for current discussions of industrial emissions scenarios leading to the stabilization of CO_2 levels above preindustrial values (*2*). Studies based on observations, energy balance models, temperature reconstructions, and global climate models (GCMs) (*3*–*13*) have found that the probability density distribution of ΔT is peaked in the range $2.0°C \leq \Delta T \leq 4.5°C$, with a long tail of small but finite probabilities of very large temperature increases. It is important to ask what determines this shape and, in particular, the high ΔT tail, and to what extent we can decrease the distribution width.

Climate consists of a set of highly coupled, tightly interacting physical processes. Understanding these physical processes is a massive task that will always be subject to uncertainty. How do the uncertainties in the physical processes translate into an uncertainty in climate sensitivity? Explanations for the range of predictions of ΔT, summarized in (*14*), have focused on (i) uncertainties in our understand-

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ing of the individual physical processes (in particular, those associated with clouds), (ii) complex interactions among the individual processes, and (iii) the chaotic, turbulent nature of the climate system, which may give rise to thresholds, bifurcations, and other discontinuities, and which remains poorly understood on a theoretical level. We show here that the explanation is far more fundamental than any of these.

We use the framework of feedback analysis (*15*) to examine the relationship between the uncertainties in the individual physical processes and the ensuing shape of the probability distribution of ΔT. Because we are considering an equilibrium temperature rise, we consider only time-independent processes.

Let $\Delta T = \lambda \Delta R_f$, where λ is a constant. In the absence of feedback processes, climate models show $\lambda \equiv \lambda_0 = 0.30$ to 0.31 [K/(W/m^2)] (where λ_0 is the reference climate sensitivity) (*16*), giving an equilibrium increase $\Delta T_0 \approx 1.2$°C in response to sustained $2 \times CO_2$. Because of atmospheric processes, however, the climate sensitivity has a value $\Delta T \neq \Delta T_0$. Conceptually, the forcing ΔR_f produces a temperature change ΔT, which induces changes in the underlying processes. These changes modify the effective forcing, which, in turn, modifies ΔT. We assume that the total change in forcing resulting from these changes is a constant C times ΔT. Thus, $\Delta T = \lambda_0 (\Delta R_f + C\Delta T)$, or

$$\frac{\Delta T}{\Delta R_f} \equiv \lambda = \frac{\lambda_0}{1 - f} \qquad (1)$$

Here, the total feedback factor $f \equiv \lambda_0 C$ (*15*). Clearly, the gain $G \equiv \Delta T/\Delta T_0 > 1$ if $f > 0$, which appears to be the case for the climate system. The range $2°C \leq \Delta T \leq 4.5°C$ corresponds to $1.7 \leq G \leq 3.7$ and $0.41 \leq f \leq 0.73$. Under our definitions, the feedback factors for individual processes are linearly additive, but the temperature changes, or gains, from individual processes are not [see the supporting online material (SOM)].

The uncertainties in measurements and in model parameterizations can be represented as uncertainties in f. Let the average value of f be $\overline{f}$ and let its SD be σ_f, the sum of uncertainties from all the component feedback processes. σ_f can be interpreted in three ways: uncertainty in understanding physical processes, uncertainty in observations used to evaluate $\overline{f}$, and, lastly, inherent variability in the strengths of the major feedbacks. If σ_f is fairly small, we see from Eq. 1 that the uncertainty in the gain, δG, is

$$\delta G \approx \frac{1}{(1 - \overline{f})^2} \sigma_f \equiv (\overline{G})^2 \sigma_f \qquad (2)$$

Thus for $\overline{G} \approx 3$ (corresponding to $\overline{\Delta T} \approx 3.6$°C), uncertainties in feedbacks are magnified by almost an order of magnitude in their effect on the uncertainties in the gain. A second point is that even if σ_f is not large, δG will be large if $\overline{f}$ approaches 1: Uncertainty is inherent in a system where the net feedbacks are substantially positive.

Finally, Eq. 2 shows that it is the sum of all the uncertainties in the feedbacks that determines δG; the uncertainties in the large positive feedbacks are not more important than the others. For example, a compilation of values of the feedback factors extracted from several GCMs (*17*) finds considerable intermodel scatter in the albedo feedback, and although the average magnitude of this feedback is not high, this scatter has an important impact on the uncertainty in the total climate sensitivity.

We now derive the shape of the distribution $h_T(\Delta T)$: the probability density that the climate sensitivity is ΔT. The important

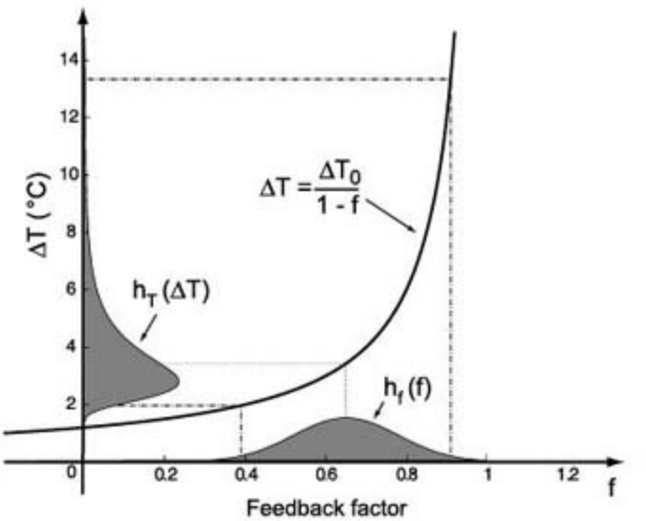

Fig. 1. Demonstration of the relationships linking $h_T(\Delta T)$ to $h_f(f)$. ΔT_0 is the sensitivity in the absence of feedbacks. If the mean estimate of the total feedbacks is substantially positive, any distribution in $h_f(f)$ will lead to a highly skewed distribution in ΔT. For the purposes of illustration, a normal distribution in $h_f(f)$ is shown with a mean of 0.65 and a SD of 0.13, typical to that obtained from feedback studies of GCMs (*17*, *18*). The dot-dashed lines represent 95% confidence intervals on the distributions. Note that values of $f \geq 1$ imply an unphysical, catastrophic runaway feedback.

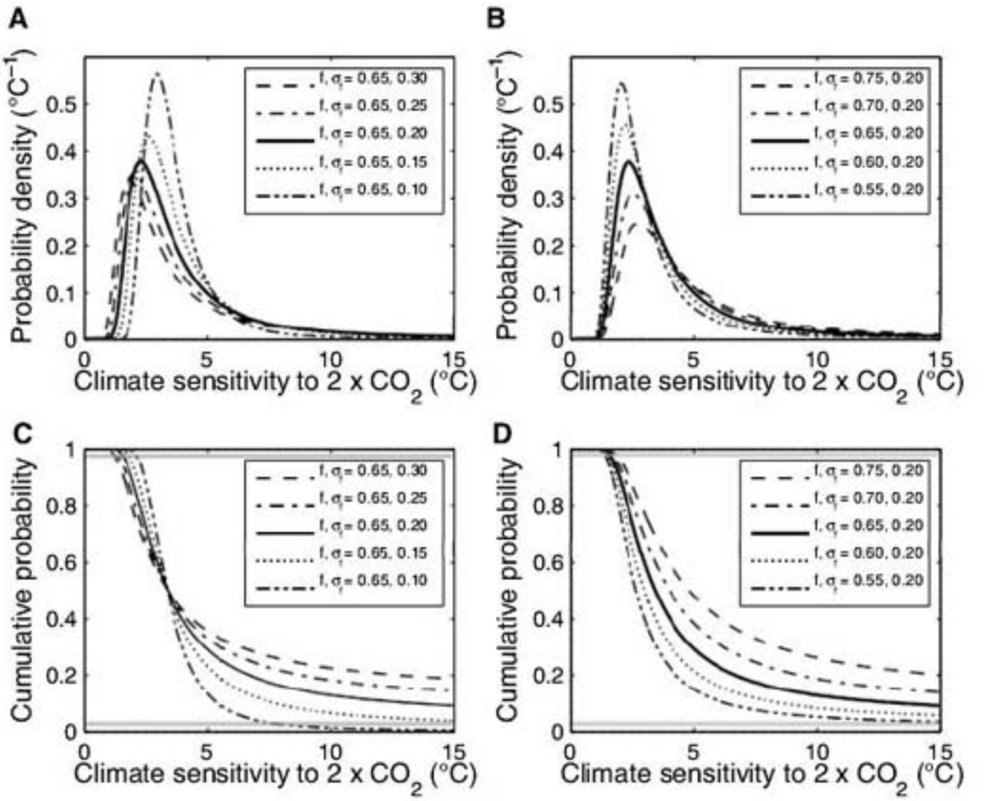

Fig. 2. Probability density distributions (**A** and **B**) and cumulative probability distributions (**C** and **D**) for climate sensitivity, calculated from Eq. 3, for a range of $\overline{f}$ and σ_f. In (C) and (D), the gray lines bound the 95% confidence interval. The peak and the shape of the density distributions are sensitive to both $\overline{f}$ and σ_f only for $\Delta T \leq \approx 5$°C. The cumulative distributions show 50% probability that $\Delta T \geq 1/(1 - \overline{f})$, independent of σ_f, and there is little dependence on σ_f of the probability that $\Delta T > \approx 10$°C. These features of the distributions imply that diminishing σ_f will have a relatively small impact on uncertainties in sensitivity estimates. See also SOM.

features of this distribution are the location of its peak and the shape and extent of the distribution at large ΔT. We focus on the relationships between these features and the parameters of the feedback distribution, $\bar{f}$ and σ_f.

Figure 1 is a schematic picture of the relationships linking $h_T(\Delta T)$ to $h_f(f)$, the probability distribution of f. The reason for the long tail of typical climate sensitivity distributions is immediately evident [see also (*3*)]. Uncertainties in climate processes, and hence feedbacks, have a very asymmetric projection onto the climate sensitivity. As the peak in the $h_f(f)$ distribution moves toward $f = 1$, the probability of large ΔT also grows. The basic shape of $h_T(\Delta T)$ is not an artifact of the analyses or choice of model parameters. It is an inevitable consequence of a system in which the net feedbacks are substantially positive.

Formally, $h_T(\Delta T)$ is related to $h_f(f)$ by the relationship $h_T(\Delta T) = h_f(f(\Delta T))(df/d\Delta T) = \Delta T_0/(\Delta T)^2 h_f(1 - \frac{\Delta T_0}{\Delta T})$. As is commonplace, we assume the errors in the feedback factors are normally distributed: $h_f(f) = (\frac{1}{\sigma_f\sqrt{2\pi}})exp\left[-\frac{1}{2}\left(\frac{(f-\bar{f})}{\sigma_f}\right)^2\right]$. Although the general features of our results do not depend on this assumption, it facilitates our analysis. Then,

$$h_T(\Delta T) = \left(\frac{1}{\sigma_f\sqrt{2\pi}}\right)\frac{\Delta T_0}{\Delta T^2} \times exp\left[-\frac{1}{2}\left(\frac{(1-\bar{f}-\frac{\Delta T_0}{\Delta T})}{\sigma_f}\right)^2\right] \quad (3)$$

Equation 3 shows how uncertainties in feedbacks lead to uncertainty in the response of a system of linear feedbacks. It can be shown that it is algebraically equivalent to a Bayesian derivation of a "posterior" distribution $h(\Delta T)$ based on a uniform previous distribution on feedbacks (SOM). As noted above, several studies have described climate sensitivity distributions similar in form to that indicated in Fig. 1 (*4*–*13*), but the particular power of Eq. 3 is that it provides a simple interpretation of the shape of these distributions. It is also a function that maps uncertainties in feedback processes onto uncertainties in climate sensitivity and therefore permits an analysis of its parametric dependencies. Figure 2 shows $h_T(T)$ and $p_{cum}(\Delta T_c)$, the cumulative probability that the climate sensitivity ΔT will exceed a given threshold, ΔT_c, for a range of values of $\bar{f}$ and σ_f. From Eq. 3, it can be shown that, for all σ_f, half the area under the curve occurs for $\Delta T < \Delta T_{0.5}$. Decreasing either σ_f or $\bar{f}$ concentrates the distribution around $\Delta T = \Delta T_{0.5}$.

The cumulative probability distributions show that decreasing σ_f or $\bar{f}$ steadily reduces the cumulative probability of large climate changes (e.g., $\Delta T \geq 8$°C). However, the probability that ΔT lies in the interval immediately outside the range of the Intergovernmental Panel on Climate Change (IPCC) (say, 4.5°C $\leq \Delta T \leq$ 8°C) is very insensitive to σ_f and $\bar{f}$ and changes little with ΔT_c. The cumulative probability distributions (Fig. 2, C and D) are driven by the extreme tail of the $h_T(\Delta T)$ distribution, which is a consequence of our choice of a Gaussian for $h_f(f)$. Even if an $h_f(f)$ without an extreme tail is assumed, the probability distributions in the interval beyond the IPCC range remain insensitive to changes in σ_f (SOM).

Thus, foreseeable improvements in the understanding of physical processes, and in the estimation of their effects from observations, will not yield large reductions in the envelope of climate sensitivity. This relative insensitivity of the probability distributions to σ_f is also a likely reason why uncertainty in climate sensitivity estimates has not diminished substantially in the past three decades.

We next compare $h_T(\Delta T)$ from Eq. 3 with selected published distributions of climate sensi-

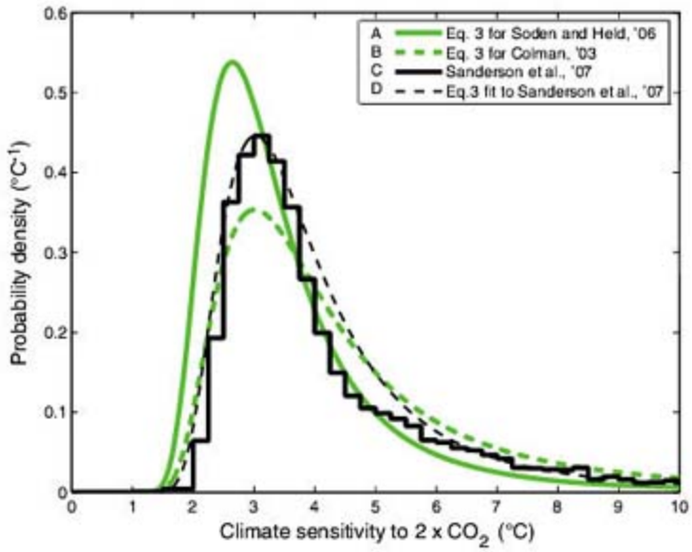

Fig. 3. Climate sensitivity distributions: (**A**) from (*18*), which calculated ($\bar{f}$, σ_f) of (0.62, 0.13) from a suite of GCM simulations; (**B**) from (*17*), which found ($\bar{f}$, σ_f) of (0.7, 0.14) from a different suite of models; and (**C**) from the ~5700-member multiensemble climateprediction.net (*9*, *10*) for different choices of cloud processes. [Data were provided courtesy of B. M. Sanderson] (**D**) Fit of Eq. 3 to the result of (*10*), which was found by estimating the mode of the probability density and its accompanying ΔT and solving for ($\bar{f}$, σ_f) from Eqs. 2 and 3, which yielded values of (0.67, 0.12).

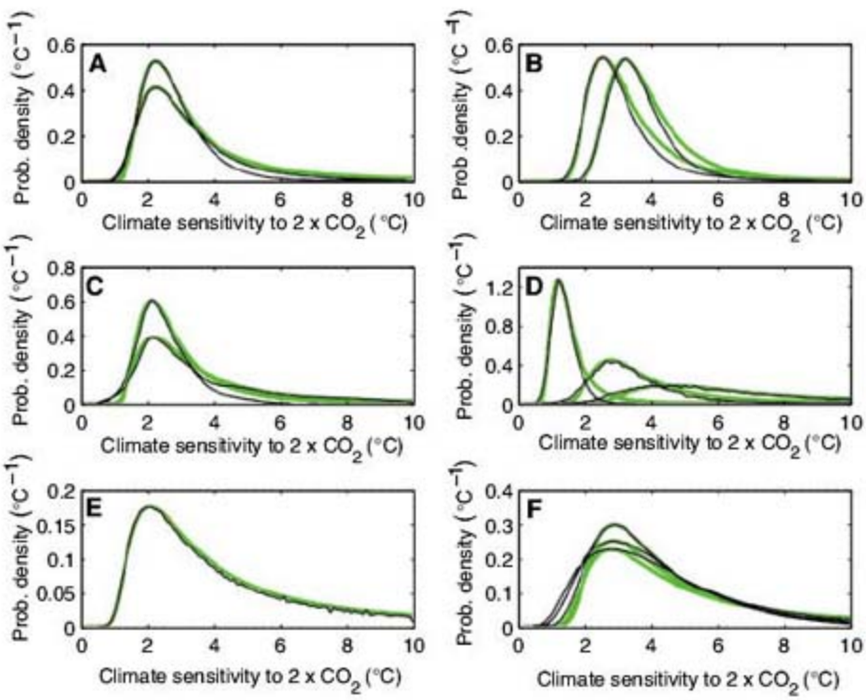

Fig. 4. Climate sensitivity distributions from various studies with the use of a wide variety of methods (black lines) and overlain with a fit of Eq. 3 (green lines), as described in Fig. 3: (**A**) from (*11*), fit with ($\bar{f}$, σ_f) = (0.58, 0.17) and (0.63, 0.21); (**B**) from (*8*), fit with ($\bar{f}$, σ_f) = (0.67, 0.10) and (0.60, 0.14); (**C**) from (*6*), fit with ($\bar{f}$, σ_f) = (0.64, 0.20) and (0.56, 0.16); (**D**) from (*4*), fit with ($\bar{f}$, σ_f) = (0.82, 0.11), (0.65, 0.14), and (0.15, 0.28); (**E**) from (*5*), fit with ($\bar{f}$, σ_f) = (0.86, 0.35) [see also (*29*)]; and (**F**) from (*12*), fit with ($\bar{f}$, σ_f) = (0.72, 0.17), (0.75, 0.19), and (0.77, 0.21).

tivity. Figure 3 shows a distribution, determined from the multi-ensemble climateprediction.net experiment, for different representations of several cloud processes (*9*, *10*). Independent estimates of feedback parameters for two different suites of GCMs (*17*, *18*) determine values for ($\overline{f}$, σ_f) of (0.70, 0.14) and (0.62, 0.13), respectively (*19*). We calculate the implied climate sensitivity distributions from Eq. 3. These match the numerically derived distributions of (*10*) quite well. We obtained a closer match by solving Eq. 3 for the $\overline{f}$ and σ_f that effectively characterize the feedback processes within the model used by (*9*, *10*) and used these parameters to generate the distribution.

Fits to several other published distributions (obtained by a wide variety of techniques), shown in Fig. 4, are also quite successful, with values $0.15 \leq \overline{f} \leq 0.86$ and $0.10 \leq \sigma_f \leq 0.35$. Some differences are seen, especially in the tail of the distributions. This is to be expected because some studies explicitly analyze the non-Gaussian distribution of uncertainties in the physics and various a priori assumptions. Nonetheless, all of these published distributions are, to a good approximation, consistent with propagation of physical-process uncertainties in a simple system of linear feedbacks.

The shape of $h_T(\Delta T)$, including its tail, is crucially dependent on the magnitude of $\overline{f}$, which we have assumed is independent of ΔT. Is there any chance that, as warming continues, the probability of extreme values of ΔT will actually diminish? This might result if the feedback factors are functions of temperature. We have performed a preliminary analysis of the changes in the $h_T(\Delta T)$ distribution that would result from adding nonlinear terms in the Stefan-Boltzmann and water vapor feedbacks (SOM). This analysis shows that these second-order effects are equivalent to decreasing $\overline{f}$ by about 0.01 to 0.02, the small effect of which can be gauged from the curves in Fig. 2. To remove the skewness completely would require changes in feedback strength that are about 25 times as great (SOM). Several nonlinear interactions of this strength might, however, contribute an additional $\sigma_f \sim 0.1$, which would change the particulars of a given probability distribution but not its fundamental characteristics. The identification and quantification of these nonlinear interactions are enormously harder tasks than the analysis of the linear feedbacks. It may be that a practical limit to the predictability of climate sensitivity should be anticipated.

It is tempting to speculate on what we can learn about the extreme tail of $h_T(\Delta T)$ from paleoclimate data. For instance, Eq. 3 can be extended to evaluate how uncertainties in reconstructions of past temperatures and net radiative forcing propagate to uncertainties in feedback strengths. Moreover, the data that we have on extreme climates [for example, the Eocene warmth and Proterozoic "snowball Earth" (*20*, *21*)] suggest that the climate system may have been acutely sensitive to radiative forcing during some intervals of Earth's history. Our results imply that dramatic changes in physical processes are not necessary for dramatic changes in climate sensitivity, provided that those changes in processes can all align in the same direction toward increased sensitivity. These are events of low but not zero probability.

Despite the enormous complexity of the climate system, the probability distribution of equilibrium climate sensitivity is well characterized by Eq. 3, which reflects the straightforward, compounding effect of essentially linear feedbacks and depends on only the two parameters $\overline{f}$ and σ_f. We have shown that the uncertainty in the climate sensitivity in $2 \times CO_2$ studies is a direct and general result of the fact that the sum of the underlying climate feedbacks is substantially positive. Our derivation of $h_T(\Delta T)$ did not depend on nonlinear, chaotic behavior of the climate system and was independent of details in cloud and other feedbacks. Equation 3 appears to explain the range of climate sensitivities reported in previous studies, which are well synthesized by the IPCC (*1*). Furthermore, reducing the uncertainty in individual climate processes has little effect in reducing the uncertainty in climate sensitivity. We do not therefore expect the range presented in the next IPCC report to be greatly different from that in the 2007 report. On the basis of the values of $\overline{f}$ and σ_f compiled from our analysis of a large number of published results, it is evident that the climate system is operating in a regime in which small uncertainties in feedbacks are highly amplified in the resulting climate sensitivity. We are constrained by the inevitable: the more likely a large warming is for a given forcing (i.e., the greater the positive feedbacks), the greater the uncertainty will be in the magnitude of that warming.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5850/629/DC1
SOM Text
Fig. S1
References

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Thermokarst Lakes as a Source of Atmospheric CH_4 During the Last Deglaciation

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Polar ice-core records suggest that an arctic or boreal source was responsible for more than 30% of the large increase in global atmospheric methane (CH_4) concentration during deglacial climate warming; however, specific sources of that CH_4 are still debated. Here we present an estimate of past CH_4 flux during deglaciation from bubbling from thermokarst (thaw) lakes. Based on high rates of CH_4 bubbling from contemporary arctic thermokarst lakes, high CH_4 production potentials of organic matter from Pleistocene-aged frozen sediments, and estimates of the changing extent of these deposits as thermokarst lakes developed during deglaciation, we find that CH_4 bubbling from newly forming thermokarst lakes comprised 33 to 87% of the high-latitude increase in atmospheric methane concentration and, in turn, contributed to the climate warming at the Pleistocene-Holocene transition.

Methane is an important greenhouse gas, whose sources to the atmosphere during the last deglaciation have yet to be reconciled with geological and paleoecological evidence. In northern high latitudes, ice-core records show that abrupt (decadal-scale) increases in temperature and precipitation were followed by a slower (100- to 300-year) rise in atmospheric methane concentration (AMC) (*1*–*3*), likely reflecting a lag in the terrestrial ecosystem response to rapid climate change. Values of the interpolar methane gradient, an indicator of the latitudinal distribution of CH_4 sources computed from the difference in CH_4 concentration between ice cores from Greenland and Antarctica, suggest that a new arctic/boreal source contributed substantial amounts of CH_4 from 14 thousand calendar years before present (kyr B.P.) through the Younger Dryas (YD) (~13 to 11.5 kyr B.P.) and accounted for >30% (30 to 40 Tg CH_4 $year^{-1}$) of the rapid rise of CH_4 emissions (83 to 99 Tg CH_4 $year^{-1}$) during the early Holocene (11.5 to 9.5 kyr B.P.) (*1*–*5*).

Two main hypotheses have been advanced to explain millennial-scale variations in AMC: a catastrophic release of methane hydrates in seafloor sediments ["clathrate gun hypothesis" (*6*)] and an increased CH_4 emission from northern wetlands in response to climate warming [wetland hypothesis (*7*–*9*)]. Reservations remain in the literature about attributing early Holocene CH_4 to a single source (*3*, *4*, *10*–*12*). Recent evidence of widespread northern peatland formation during the early Holocene suggests that wetlands may have contributed 4 to 9 Tg CH_4 $year^{-1}$ (*8*, *9*). There is a marked paucity of peatland initiation dates for the vast region of north Asia that was not ice-covered during the Last Glacial Maximum (LGM) (*9*). It was in the lowland areas of this region that an extensive initiation of deep "thermokarst" lakes occurred at the beginning of the last deglaciation [(*13*–*15*) and table S1] and may have been a source of atmospheric CH_4 at that time (*16*). When ice-rich frozen ground thaws, the loss of volume from melting ice creates depressions in the land surface: a process called thermokarst (*13*). Ponding of water in depressions creates thermokarst lakes, which may expand as a result of both thermal and mechanical erosion over time scales of decades to centuries (*13*).

We develop this third alternative hypothesis (thermokarst-lake hypothesis): CH_4 ebullition (bubbling) from newly formed thermokarst lakes occurred extensively across large unglaciated regions in northern high latitudes, particularly in Siberia, as the climate became warmer and wetter. Thermokarst-lake CH_4 emissions are distinct from those of wetlands because thermokarst lakes are a distinctive ecosystem type (*13*) not typically included in wetland emission estimates (*17*) and because ebullition, which dominates CH_4 emissions from thermokarst lakes, is a substantially larger source of CH_4 than previous-

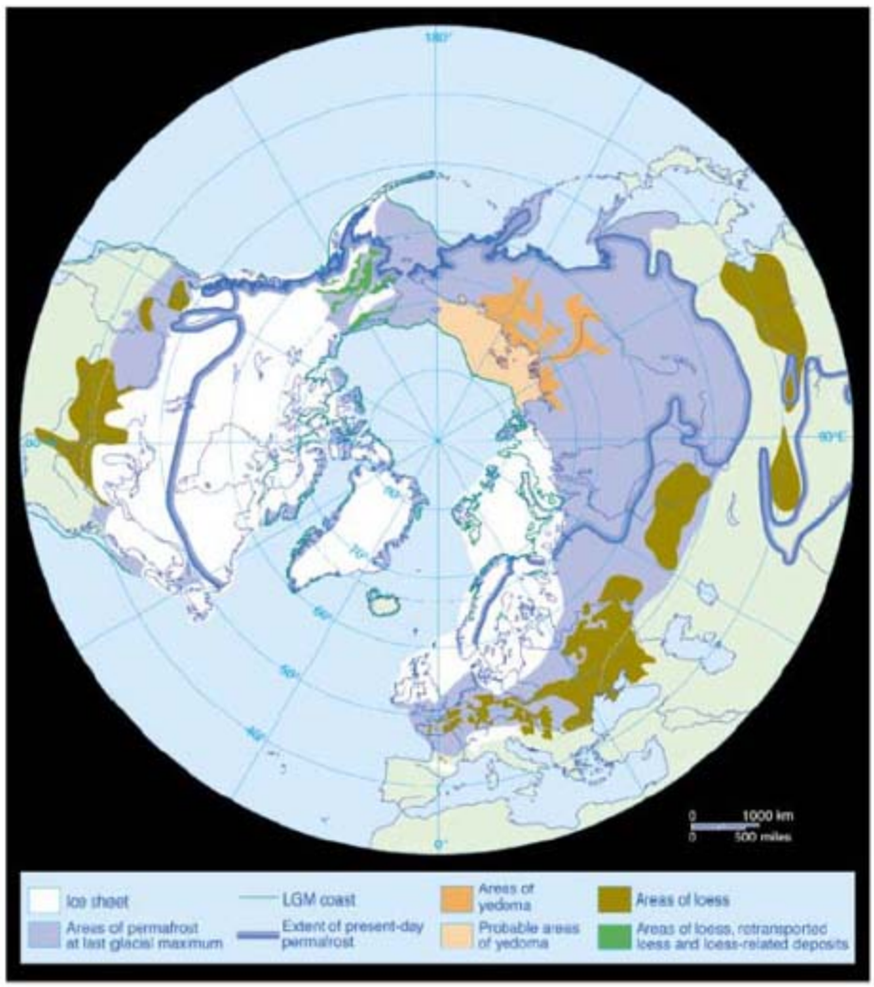

Fig. 1. Current and probable LGM regions of loess, loess-related deposits, and yedoma mapped in relation to the modern and LGM distribution of permafrost. Information sources are provided in the SOM text. Modern and LGM coasts are shown, the latter approximated from the modern 120-m isobath (*30*). The map indicates that considerable areas of loess would have been frozen at the LGM and subsequently thawed, and yedoma would have extended northward on the exposed Siberian shelf.

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ly thought (*18*). We provide three lines of evidence in support of this hypothesis: (i) A reconstruction of late Quaternary paleogeography documents the areal extent over which this process likely occurred, and a synthesis of basal radiocarbon-dated thermokarst-lake sediments indicates that many thermokarst lakes were initiated ~14 kyr B.P. and that thermokarst activity accelerated during 11.5 to 9 kyr B.P., coinciding with the CH_4 emissions increase from arctic/boreal sources; (ii) Laboratory incubations show that Pleistocene-aged frozen sediments support high rates of CH_4 production; and (iii) Thermokarst lakes that are currently expanding in areas of frozen Pleistocene sediments have high ebullition rates of Pleistocene-aged CH_4 (just as they would have had at the onset of their formation in the early Holocene). To estimate post-Pleistocene CH_4 emissions from lakes, we integrate the information on CH_4 production rates from sediments, carbon (C) loss from drained thermokarst-lake sediments that refroze, flux rates from modern thermokarst lakes, and the areal extent of Pleistocene sediments subject to thermokarst-lake development. We show that these emissions could have contributed up to ~87% of the boreal contribution to AMC increases recorded in ice cores.

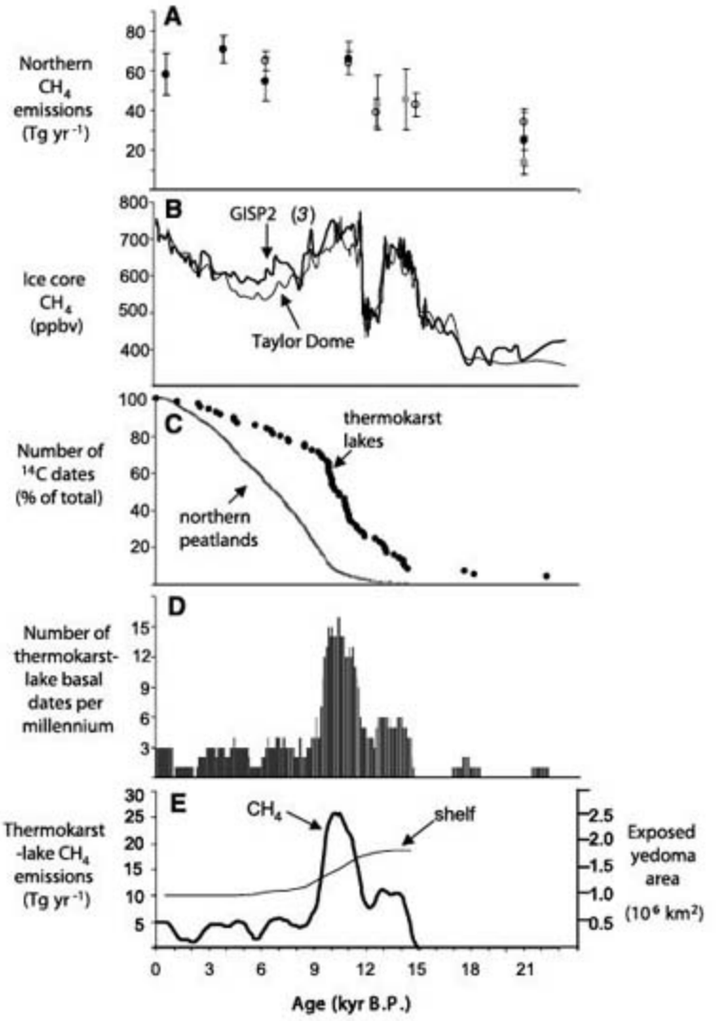

Fig. 2. Thermokarst-lake development during deglaciation as a northern source of atmospheric CH_4. **(A)** Three independent estimates of Northern Hemisphere CH_4 emissions derived from the interpolar CH_4 gradient [open circles (*3*), solid black circles (*4*), and solid gray circles (*5*)] suggest that a modest northern CH_4 source appeared by ~14 kyr B.P., was sustained through the YD, and increased substantially after 11.5 kyr B.P. Error bars indicate uncertainties in three-box models propagated from SEs in CH_4 concentrations in ice cores for selected time intervals and uncertainties in the calculation of the interpolar CH_4 difference. **(B)** The interpolar CH_4 gradient is modeled based on the difference in ice-core CH_4 concentrations in Greenland [Greenland Ice Sheet Project 2 (GISP2), black line] and Antarctica (Taylor Dome, gray line) (*3*). The AMC drop recorded during the YD in these global records is attributed to decreases in tropical (as opposed to northern) CH_4 sources (*4*, *5*). ppbv, parts per billion by volume. **(C** and **D)** The pattern of northern hemisphere CH_4 emissions in (A) is consistent with the formation of CH_4-emitting northern thermokarst lakes shown as a cumulative curve (C) and as the number of documented thermokarst-lake initiation dates per millennium occurring within time steps of 100 ± 500 calendar years B.P. according to table S1 (D). The cluster of lakes initiated between 11.5 to 9 kyr B.P. coincides with the steepest part of the cumulative curve of 69 thermokarst initiation dates in (C) and with the peak of AMC recorded in ice cores after abrupt warming and wetting. The cumulative curve of 1516 peatland initiation dates from (*9*), shown also in (C), suggests that northern peatlands would also have been a source of early Holocene atmospheric CH_4, though acceleration of peatland initiation lags behind that of thermokarst lakes by several millennia. **(E)** Methane emissions for the Siberian yedoma region, modeled according to rates of thermokarst activity, suggest that the expansion of yedoma thermokarst lakes on the exposed yedoma surface could have released as much as 20 to 26 Tg CH_4 $year^{-1}$ after abrupt warming around 11.5 kyr B.P. The curve labeled "shelf" indicates the decline in the area of yedoma exposed on the continental shelf as sea level rose during the early Holocene. The text describes a second independent scenario that yields the estimate of early Holocene thermokarst-lake emissions (13 to 20 Tg CH_4 $year^{-1}$). Together, these scenarios suggest that thaw of yedoma would have been an immediate and substantial contribution to the new boreal CH_4 source (~30 to 40 Tg $year^{-1}$) observed in ice-core records.

During the late Pleistocene, extensive loess and loess-related deposits formed throughout unglaciated regions of northeast Siberia, Europe, and North America (Fig. 1). In northeast Siberia, these deposits, which have a particularly high ice content and a large volume of labile organic C, are referred to as the "yedoma ice-complex" [(*19*–*22*) and supporting online material (SOM)]. Yedoma has remained largely frozen throughout the Holocene, currently occupies an area of >1 × 10^6 km^2, and in many regions is tens of meters thick (*14*, *21*). During the LGM, when the global sea level was 120 m lower than that of today, similar deposits covered substantial areas (0.9 × 10^6 km^2) of the exposed northeast Eurasian shelves (*19*, *22*) (Fig. 1).

In northeast Siberia, thaw of yedoma makes organic matter available in anaerobic lake bottoms, fueling methanogenesis (*18*, *23*). Once initiated, thermokarst lakes deepen and can persist for thousands of years (*13*, *14*, *24*) (SOM text). In certain areas of Siberia and northern Alaska where thermokarst lakes are prominent, as much as 50% of the landscape is covered with lake scars (*13*, *25*, *26*). In several major Siberian lowlands, nearly 100% of the yedoma ice-complex has been reworked by lakes (*13*, *14*).

Patterns of thermokarst-lake formation based on a compilation of basal radiocarbon dates appear broadly consistent with the climate evolution of northeast Siberia, Alaska, and northwestern Canada, as well as with patterns of increase in boreal CH_4 sources to the atmosphere after the LGM (Fig. 2). There are few records of thermokarst during the glacial period. Data suggest that thermokarst-lake formation occurred as early as ~14 kyr B.P. in Russia, Alaska, and northwestern Canada (table S1), coincident with increases in boreal CH_4 sources, temperature, and moisture (*27*). Some data suggest a climate reversal at the time of the YD, but its expression is greatly muted in northeast Siberia and Alaska when compared with the Greenland temperature record (*15*, *27*–*29*). Geological evidence suggests that thermokarst lakes persisted (*14*) and continued to form through the YD, which is consistent with sustained sources of boreal CH_4 (Fig. 2). Multiple proxies indicate that the warmest period of the current interglacial in northeast Siberia (11 to 9 kyr B.P.) occurred in concert with peak summer insolation (*27*, *28*). During this period, many new thermokarst lakes formed in Siberia (Fig. 2, C and D); 45% of the compiled dates of thermokarst-lake formation fall between 11.5 to 9 kyr B.P. (table S1). Subsequently, the number of reported dates decreases throughout the Holocene, as relatively stable drainage patterns became established. Thermokarst lakes continue to develop today as evidenced, for example, by remote sensing analyses of a yedoma area in northeast Siberia that shows a ~14% increase in lake area during recent decades (*18*).

Until recently, thermokarst lakes were not recognized as a globally important source of atmospheric CH_4. Bubbling from thermokarst lakes, which currently cover a large proportion (>10%) of yedoma territory in Siberia, contributes ~4 Tg CH_4 annually to regional sources (*18*, *23*). Given the extensive degradation of yedoma permafrost since the LGM (Fig. 1), observed CH_4 emissions from lakes associated with yedoma degradation today, and geological evidence of thermokarst-lake formation at the start of the Holocene (Fig. 2), we propose that CH_4 bubbling from Siberian thermokarst lakes contributed substantially to the rapid increases in AMC during deglaciation (*22*).

To assess this thermokarst-lake hypothesis, we applied rates of CH_4 emissions measured in modern thermokarst lakes to the pattern of post-LGM lake development implied by basal-date records that serves as a proxy for thermokarst activity, as a function of exposed yedoma terrain in 1000-year time steps during deglaciation (fig. S1). Details of measured parameters and transfer functions are given in (*30*). In this scenario, thermokarst lakes appeared on the exposed yedoma land surface in northeast Siberia between 14 to 13 kyr B.P., contributing ~11 Tg CH_4 $year^{-1}$. Lake emissions of ~8 to 9 Tg CH_4 $year^{-1}$ continued through the YD until 11.5 kyr B.P., when a spike in basal dates represents an acceleration of thermokarst activity and new lake formation, contributing up to 26 Tg CH_4 $year^{-1}$. After 9 kyr B.P., our scenario depicts a decline in lake emissions as thermokarst activity decelerated and total yedoma area available for new thermokarst continued to decrease. Average lake emissions from 9 kyr B.P. to the present were 2 to 6 Tg CH_4 $year^{-1}$. Our calculations do not include CH_4 that would have been released from CH_4-producing submarine habitats created by sea-level rise or from North American lakes (*14*, *22*).

We provide a second independent estimate of CH_4 emissions using C mass balance based on the C lost from yedoma beneath former thermokarst lakes (*30*). Yedoma beneath thermokarst lakes that formed in the Holocene and subsequently drained and refroze has ~33% less C [18.0 ± 1.4 kg C m^{-3} (mean ± SE), n = 15 samples] than yedoma that never thawed (26.8 ± 1.5 kg C m^{-3}, n = 54 samples) (*18*). At the beginning of the Holocene, yedoma contained ~500 Gt C (*26*). Assuming that if 15 to 25% of the yedoma C beneath lakes, whose scars cover 50% of the yedoma territory, was emitted as CH_4 (*21*, *23*) during the Holocene and that if 65% of these emissions occurred between 14 to 9 kyr B.P., based on geological evidence (table S1), then thawing yedoma beneath lakes would have contributed (on average) 8 to 12 Tg CH_4 $year^{-1}$ during deglaciation. This estimate is conservative because it ignores Holocene organic detritus accumulating on lake bottoms (*31*) that would also produce CH_4. Pleistocene-aged organic C fuels ~60% of the CH_4 emitted from modern yedoma thermokarst lakes in northern Siberia (*18*), suggesting that contributions of Holocene substrates for methanogenesis could also have been large (~40%), yielding a total lake-emissions estimate of 13 to 20 Tg CH_4 $year^{-1}$.

Finally, we used CH_4 production potentials (145 ± 31 g CH_4 m^{-3} $year^{-1}$, n = 23 samples) of thawed northern Siberian yedoma in laboratory incubations to provide an additional independent confirmation of thawing yedoma contributions to the AMC rise at the onset of this interglacial period (*30*). Based on (*32*), if we assume that abrupt warming and wetting transformed 10% of the dry, unglaciated landscape (1.9×10^6 km^2) into a ponded surface regime dominated by shallow pools for 3 to 4 months of the year, then anaerobic decomposition in the surface (1-m depth) of the locally deepening active layer might have produced CH_4 on the order of 7 to 9 Tg $year^{-1}$. Although microbial oxidation in pools might have reduced total CH_4 emissions during the early stages of pond formation, our incubation-based calculation demonstrates that the CH_4 production potential of yedoma sediments was high enough to contribute immediately upon thaw to the abrupt rise in AMC.

Our two independent estimates (20 to 26 and 13 to 20 Tg CH_4 $year^{-1}$) of yedoma thermokarst-lake contributions to the rise in AMC are similar to one another and within the ~30 to 40 Tg CH_4 $year^{-1}$ boreal-source constraint from the interpolar CH_4 gradient recorded in ice cores (*4*). Formation and expansion of thermokarst lakes at the onset of Holocene warming appear to have led to a large new AMC source: bubble emissions from lakes. Our estimate of CH_4 derived largely from the Pleistocene-aged C reservoir can account for a substantial proportion (33 to 87%) of northern AMC sources during the last deglaciation. If this conservative estimate is roughly correct, other northern sources [such as peatlands (*8*, *9*), hydrates, and/or wildfires, or natural gas seeps (*11*, *12*)] are also required as inputs to AMC during deglaciation. Isotope ratios of $^{13}C/^{12}C$ of CH_4 [–58 to –83‰ (per mil)] and D/H (–338 to –420‰) from modern Siberian thermokarst lakes (*18*) are similar to those of boreal wetlands and are consistent with multisource scenarios proposed to explain CH_4 isotope ratios in ice cores during the latest deglaciation [(*11*, *12*) and SOM text].

Records of AMC in ice cores show that a moderate arctic/boreal source appeared at 14.8 kyr B.P. and was sustained throughout the YD (*5*). In the early Holocene, there was a rapid rise in boreal emissions that demands a rapid ecosystem response. Estimates of early peatland emissions are insufficient to account for this northern source alone (*9*). Here we provide a first approximation of paleo-CH_4 flux from a new terrestrial source, based on what is known about patterns of yedoma thermokarst-lake ebullition emissions and the timing of thermokarst-lake formation during deglaciation. Our compilation of thermokarst-lake basal ages suggests that lakes formed extensively in Alaska, northwestern Canada, and Russia as early as 14 kyr B.P. Thermokarst lakes would have contributed modestly to atmospheric CH_4 through the YD, explaining the overshoot in AMC relative to temperature in ice core records during the YD (*33*). Finally, an expansion of thermokarst lakes in the early Holocene contributed considerably to the spike in AMC recorded in ice cores.

About 500 Gt C remain preserved in the yedoma ice-complex in northeast Siberia (*21*). If the yedoma territory with its high ice–content permafrost warms more rapidly in the future, as projected (*34*), ebullition from thermokarst lakes could again become a powerful positive feedback to high-latitude warming, as it appears to have been during deglacial climate warming at the onset of the Holocene. Expansion and formation of yedoma thermokarst lakes in northeast Siberia during the era of satellite observations suggest that this positive feedback is already underway (*18*). This important source of atmospheric CH_4 is not currently considered in climate-change projections.

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Holocene. However, CH_4 emissions are not well known for lakes in these regions and are not included in our thermokarst-lake CH_4 emission estimate. Our calculations of CH_4 emission from thermokarst lakes are based on a conservative estimate of the extent of yedoma, namely its current distribution in north Siberia and the previously exposed adjacent continental shelves (total area: 1.9×10^6 km^2 at 15 kyr B.P.). Additional details are provided in the SOM Materials and Methods.

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Supporting Online Material

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The Coevolution of Parochial Altruism and War

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Altruism—benefiting fellow group members at a cost to oneself—and parochialism—hostility toward individuals not of one's own ethnic, racial, or other group—are common human behaviors. The intersection of the two—which we term "parochial altruism"—is puzzling from an evolutionary perspective because altruistic or parochial behavior reduces one's payoffs by comparison to what one would gain by eschewing these behaviors. But parochial altruism could have evolved if parochialism promoted intergroup hostilities and the combination of altruism and parochialism contributed to success in these conflicts. Our game-theoretic analysis and agent-based simulations show that under conditions likely to have been experienced by late Pleistocene and early Holocene humans, neither parochialism nor altruism would have been viable singly, but by promoting group conflict, they could have evolved jointly.

Late 19th-century scientists as diverse as Charles Darwin (*1*) and Karl Pearson (*2*) recognized war as a powerful evolutionary force that might foster social solidarity and altruism toward the fellow members of one's group. But despite Hamilton's speculation about how this could occur (*3*), neither the process by which war might have become sufficiently common to support the evolution of altruism nor the possibility that altruism conditioned on group membership might have contributed to the unusually high level of lethal intergroup conflict among humans has been subjected to systematic investigation.

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The empirical importance of both altruism and hostility to members of other groups is well established. Experimental and other evidence demonstrates that individuals often willingly give to strangers, reward good deeds, and punish individuals who violate social norms, even at a substantial personal cost (*4*), while favoring fellow group members over "outsiders" in the choice of friends, exchange partners, and other associates and in the allocation of valued resources (*5*). For example, a recent "third party punishment" experiment in Papua New Guinea revealed strong favoritism toward a subject's own linguistic group in giving to others, and significantly greater punishment of individuals from another linguistic group (by comparison to the subject's own group) who acted ungenerously toward the subject's fellow group members (*6*).

Intergroup hostility and aggression are similar to altruism in that an individual adopting these behaviors incurs mortal risks or foregoes beneficial opportunities for coalitions, co-insurance, and exchange, thereby incurring a fitness loss by comparison to those who eschew hostility toward other groups. When this is the case, and when the members of the actor's group benefit as a result of one's hostile actions toward other groups, we term the behavior "parochial altruism." The experimental subjects in Papua New Guinea provide an example.

Neither parochialism nor altruism would seem likely to survive any selection process that favors traits with higher payoffs. But parochial altruism could have emerged and proliferated among early humans because our ancestors lived in environments in which competition for resources favored groups with substantial numbers of parochial altruists willing to engage in hostile conflict with outsiders on behalf of their fellow group members. These group benefits could have offset the within-group selection against both parochialism and altruism. Unlike multilevel selection models in which group conflict is simply assumed (*7*–*9*), we thus provide an explanation of warfare itself and its uniquely lethal nature among humans. Whether this account is plausible is an empirical question.

The ethnographic and archaeological record suggests that warfare was a frequent cause of death among some hunters-gatherer groups and early tribal societies (*10*, *11*). Mortality in intergroup conflicts as a fraction of all deaths may have been an order of magnitude greater among early humans than among Europeans during the bellicose 20th century. Most hostile intergroup contact was probably ongoing or intermittent, with occasional casualties, more akin to boundary conflicts among chimpanzees (*12*) than to modern warfare. However, "pitched battles" did occur

among foragers, as in the conflict between two coalitions of aboriginal Australians involving around 700 combatants (*13*). As natural disasters and periodic resource scarcity have been identified as the most important correlates of warfare among forager groups (*14*), it seems likely that the volatile climate of the late Pleistocene (from about 125,000 until 10,000 years before the present) contributed to high levels of intergroup conflict. Groups that avoided hostile interactions benefited from greater access to the resources in what would otherwise have been nonproductive defensive buffer zones (*15*, *16*), as well as from between-group risk sharing (*17*) and exchange (*18*), often over substantial distances [see also (*19*)].

Could parochial altruism have emerged and proliferated in this environment? We model the evolution of genetically transmitted behavioral types in a population of foragers who engage in both within- and between-group interactions. Individuals may be altruistic (or not) and parochial (or not). We represent these behaviors as the expression of two hypothetical alleles at each of two loci. There are thus four types: parochial altruists (PA, that is bearers of the P and A alleles), tolerant (nonparochial) altruists (TA), parochial nonaltruists (PN), and tolerant nonaltruists (TN). Parochials (of either type) are hostile toward other groups. But only parochial altruists engage in combat, because the nonaltruists are not willing to risk death in order to benefit their fellow group members. In the absence of between-group hostility, tolerant members of a group benefit from the above-mentioned mutually advantageous interactions with other groups.

Two types of selection are at work in the model to be presented. Within-group selection favors tolerant nonaltruists and tends to eliminate parochial altruists (as well as tolerant altruists and parochial nonaltruists). By contrast, the second process, selective extinction resulting from intergroup conflict, may favor parochial altruists despite the fact that they risk death even in victorious battles. To clarify the role of war, parochialism, and selective extinction, we do not model the other mechanism by which altruism may spread, namely, selective emigration (*20*). Thus, in the absence of territorial expansion through conquest, we assume that group size is fixed, so highly altruistic groups do not contribute more replicas to the next generation. Our setting, therefore, is quite unfavorable for the evolution of altruism because it is equivalent to models in which local density-dependent selection exactly offsets the group benefits of altruism (*21*, *22*).

Parochial altruists who survive conflicts do receive a direct individual reproductive benefit if a war occurs, because they share in their group's increased probability of winning a hostile encounter that results from their status as a "fighter" (relative to the expected outcome of the conflict had the individual been of another type). Winning a hostile encounter yields two kinds of reproductive benefits for members of a group: a greater chance of survival and (for the survivors) the opportunity to produce additional offspring to replace those killed in the losing group. However, in our simulations (*19*), the increased risk of mortality in warfare incurred by parochial altruists offsets this direct benefit by a wide margin. As a result, each parochial altruist would enjoy substantially greater expected reproductive success by switching to tolerant and/or nonaltruistic behaviors, even taking into account that the switch would increase the probability that his group would be defeated should a conflict occur. Thus, those who fight for their group are altruistic in the standard sense of the term (*23*).

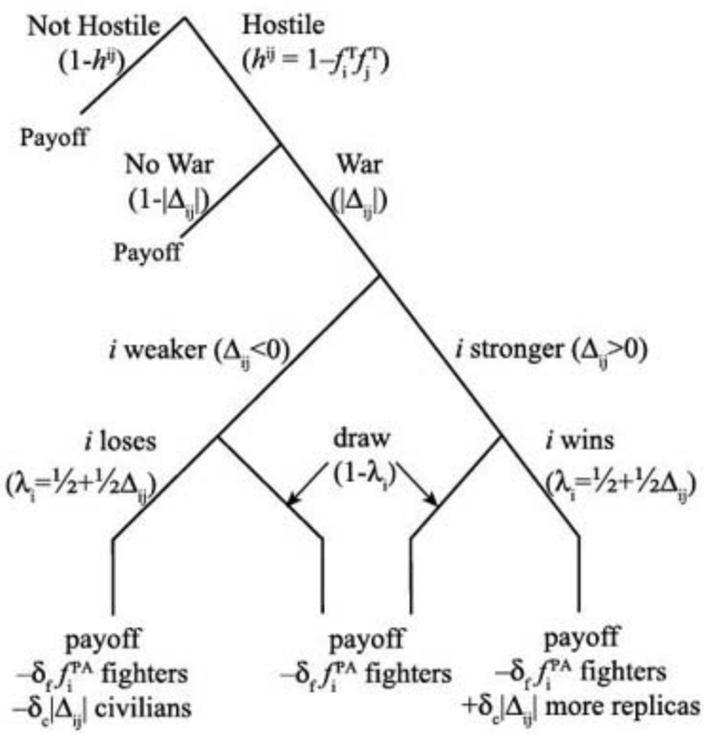

Fig. 1. Between-group interaction. Notation: f_i^T, f_j^T = the fractions who are tolerant in group i and group j, respectively; $h^{ij} = 1 - f_i^T f_j^T$ = the probability that an interaction between groups i and j will be hostile; f_i^{PA}, f_j^{PA} = the fractions who are parochial altruists in group i and j; $\Delta_{ij} = f_i^{PA} - f_j^{PA}$; $|\Delta_{ij}|$ = probability that a hostile interaction will result in a war; λ_i = the probability that group i wins the war; δ_f = the fraction of fighters (PAs) who die should a war occur (δ_f = 0.14 in our benchmark simulations) and δ_c $|\Delta_{ij}|$ = fraction of civilian mortality in the losing group (δ_c = 2.5 in our benchmark simulations). Payoff refers to the payoffs to the public goods and peaceful intergroup interactions described in Table 1.

Every generation, all members of each group are paired randomly with members of their group to produce offspring, whose expected number is proportional to the parental couple's share of the group's payoffs, described below. So as not to favor the hypothesized coevolution of parochialism and altruism that depends on the two behaviors being statistically associated, we adopt an intergenerational transmission process with no built-in tendency for the parochial and altruistic alleles to be correlated. Thus, we assume no within-group assortment in mating and we allow complete recombination (so that, e.g., a parental couple composed of a PA and a TN will have offspring of all four behavioral types with equal probability). Additionally, this process is modified by mutation: With some probability (μ), each member's offspring inherits a type randomly from the four possible types independently of the parental types. With probability ($1 - \mu$), the nonmutational replication above takes place. Each generation, with some probability (m), each member migrates to a randomly selected group.

Between-group interactions are as follows. Every generation, each group interacts with another group either cooperatively or in a hostile manner (Fig. 1). Hostility in an intergroup interaction results if the fraction of parochial members of at least one group is sufficiently great. The use of force between the two groups occurs when one of the two is sufficiently likely to win, reflecting the fact that as with other primates, evenly matched human groups seek to avoid costly conflicts (*24*). The probability that a group wins a conflict depends on the difference in the number of fighters (parochial altruists) in the two groups. If a conflict occurs, a fraction of the fighters in both groups die, and a fraction of the surviving fighters and nonfighters of the losing group are also eliminated. This civilian mortality fraction is equal to a constant times the between-group difference in the fraction of parochial altruists, so the greater is the imbalance of forces, the more severe are the fatalities of the losers. If the group with more fighters does not win, the outcome is a draw in which fighters die as above, but nonfighters do not.

Those eliminated in both groups are replaced by offspring from randomly chosen mates (as described above) in the winning group, who migrate to the losing group, bringing both groups' numbers up to the capacity of their sites. We explored (*19*) an alternative to this "migration" scenario in which the fighters of the winning group kill fewer of the losers but mate with the surviving losing population, repopulating their site in this manner. This "mating" scenario favors the evolution of parochial altruism more strongly than the results shown below as it privileges parochial altruists (because they are the fighters who mate with the losing population) in the repopulation process (by comparison with the migration scenario, in which those parenting the colonists to repopulate the losers' site are drawn randomly from the survivors among the winning population).

If the interaction is not hostile, each tolerant member receives a net benefit from each tolerant member of the paired group. Parochials receive no such benefits. As a result, in the absence of hostility, the expected payoff to the Ts in a given group exceeds that to the Ps irrespective of the fraction of Ts in the group, so T is the dominant strategy.

Individual payoffs from within-group interactions are determined as follows. In every generation at a cost c, altruists contribute to a public good whose value (b) is shared equally among the n group members belonging to a single generation. The public good may be shared information, risk-pooling, or similar behaviors. Those who are not altruistic (Ns) do not contribute. Because $b > c > b/n$, contributing raises group-average payoffs; but a contributor's payoff would be increased by an amount $c - b/n$ by not contributing, irrespective of the number of other As within the group. The result is that both As and Ps face adverse within-group selection. These payoffs are described in Table 1.

The sequence of events in each generation is as follows: Group interaction occurs, followed by repopulation of any group that suffered fatalities in warfare; members of the reconstituted groups then interact in the public goods game, after which they reproduce in proportion to their share of the group's total payoffs in the game (couples producing an average of two surviving offspring so as to maintain group size); finally, the parental generation dies and migration of the new generation occurs.

Our agent-based computer simulation explored the properties of this model under a range of parameters calibrated to resemble the environment of most late Pleistocene and early Holocene (i.e., prior to about 7000 years ago) humans (*19*). Our benchmark group size ($n = 26$ members of a single generation or a total size of about 78) could represent a coalition of three bands, each of a total size likely to have approximated a late Pleistocene band (*25*). The benchmark migration rate (25% per generation) is based on observed hunter-gatherer population movements. Our metapopulation is composed of 20 groups, giving it a total size thought to be common among late Pleistocene ethno-linguistic units.

Figure 2A gives an approximation of the explicit dynamics of the underlying Markov process, the arrows indicating selection against parochials in the absence of altruists and conversely, as expected. Figure 2B shows that as a result of this dynamic, over a very long period, the simulated population spends most of the time in states with many parochial altruists and few of the other three types, or in states with many tolerant nonaltruists and few of the other three types. In the former case, high levels of parochialism promote frequent conflicts, the victors being those groups with many parochial altruists. By contrast, when tolerant nonaltruists are prevalent, hostilities are rare, the benefits of cooperative between-group interactions are substantial, and the within-group selection pressures against parochials and altruists therefore predominate.

Statistical analysis of very many generations in which the population is near point b in Fig. 2A indicate that both altruism and parochialism are sustained by levels of intergroup conflict and deaths in warfare that are considerably below estimates from archaeological and ethnographic data relevant to late Pleistocene and early Holocene conditions (*19*). In the bellicose states near point b in Fig. 2A, 3.6% of the total population perish each generation in warfare, compared to an estimate of more than three times this number based on ethnographic and archaeological evidence (*11*). Our results thus do not require implausibly high levels of war-induced mortality.

The top and middle panels of Fig. 3 illustrate transition processes between states close to point a and those close to point b. These infrequent and abrupt transitions occur in both directions because, as a result of the random nature of matching of mates and groups, outcomes of group interactions, migration, and mutation, the population may move from the neighborhood of either point a or point b to a state where the selective forces represented by the arrows in Fig. 2A carry the population to the opposite corner of the state space. The bottom panel is a summary of states in a large number of runs. As seen in the bottom left panel, when parochial altruists are prevalent in the population, fewer wars occur because groups tend to be evenly matched. The bottom right panel shows that when wars are more frequent, there tend to be more parochial altruists in the population.

Experiments with alternative parameter values (*19*) show that the population frequency of parochial altruists and the incidence of deaths due to war vary inversely with group size and the migration rate. This is because these population structure parameters diminish the between-group differences in the distribution of types, thereby both reducing the frequency of wars and weakening the effects of selective extinction when wars do occur. War deaths and the population frequency of parochial altruists vary positively with the extent of losses inflicted on civilians among the losers. Varying the rate of mortality among fighters first increases the fraction of war deaths and then lowers it, because for very high rates of fighter mortality few parochial altruists survive in the population and few wars occur. The results are not very sensitive to plausible variations in the benefits and costs of altruism.

These results do not occur because parochial altruists directly benefit by increasing the chance that their group will prevail in a contest, as we have seen. Indeed, at most states, an individual who hypothetically switched to become a PA would incur a fitness loss larger than the cost (c) of contributing to the within-group public goods game. Nor do the two stable states (points a and b in Fig. 2A) arise because parochial altruists and tolerant nonaltruists deliberately associate with like types, as in the Eshel and Cavalli-Sforza model of "selective assortment" (*26*). Preferential assortment with close genetic kin is not involved, because groups are quite large and both migration and within-group pairing for reproduction are random.

Rather, the crucial assortment processes that account for our results arise endogenously from the pattern of intergroup relationships. When cooperative interactions among groups are common, tolerant nonaltruists proliferate because they benefit from positive assortment when groups interact (because the pairs of groups that cooperate are those in which both have many tolerant members). Correspondingly, wars are characterized by negative assortment benefiting parochial altruists because evenly matched groups avoid wars, and the wars in which most parochial altruists engage (and win) tend to be against groups with larger fractions of the other three types. Thus, the enhanced reproductive success due to increased group success in war that a parochial altruist confers on his group-mates tends to disproportionately benefit other parochial altruists, explaining their success.

We have shown that transitions from tolerant nonaltruistic and hence relatively peaceful states to parochial altruist and bellicose states can be very rapid (occurring in less than 200 generations, or about 5000 years) (Fig. 3). The markedly higher reproductive success of predominantly parochial altruist groups when interacting with groups with fewer parochial altruists could therefore explain the rapid range expansions that are thought to be common among some late Pleistocene human groups, and thus may partly explain the still puzzling second great hominid diaspora that swept from Africa as far as Australia in the course of no more than 10 millennia.

The coevolutionary dynamics of parochial altruism and war outlined here also provide a plausible explanation of the results of the behavioral experiments such as the one in Papua New Guinea mentioned above. On the basis of our model, one would expect tolerant altruists to bear costs in order to give to both insiders and outsiders, and to punish those who violate norms. In view of the importance of mutually beneficial intergroup relations, punishment of norm violators by altruists would include out-group members as well as insiders. But parochial altruists would give preferentially to their own members and punish those who harm group members more severely than if the victim is not an insider. Our model thus shows that spiteful behavior toward outsiders and the other behaviors in the experiment could have evolved by benefiting other group members when hostile intergroup contests occur. (In the experiment, punishing an outsider increases the relative payoffs of the actor's group because the cost to the target is three times the cost to the punisher.) Giving to others in the experiment—even to one's own group members—cannot be explained by kin altruism because the cost of giving was the same as the benefit to the recipient; so this kind of behavior would not be selected for even if group members were identical twins.

Finally, the model and simulations contribute to an emerging evolutionary explanation of why group boundaries so powerfully influence human behavior (*27–29*).

We have explained how *Homo sapiens* could have become a warlike yet altruistic species. But there is no evidence that the hypothetical alleles

Table 1. Expected payoffs to four behavioral types: Public goods and peaceful intergroup interactions. The fraction of group i who are altruists is f_i^A. All members receive the benefit of the public good, bf_i^A. Tolerant players of both types receive the benefits of nonhostile group interaction, gnf_j^T, where g is the benefit of nonhostile group interaction, n is group size (of a single generation), and f_j^T is the fraction of the other group who are tolerant. If the interaction is hostile, the bold entries do not apply; if no war occurs, the payoffs to parochials and tolerants are identical. Simulation benchmark values of the parameters in the table are as follows: $c = 0.01$, $b = 0.02$, $g = 0.001$, $m = 0.25$, $\mu = 0.005$, $n = 26$.

	Parochials	Tolerant
Altruist	$bf_i^A - c$	$bf_i^A - c + \mathbf{gnf_j^T}$
Nonaltruist	bf_i^A	$bf_i^A + \mathbf{gnf_j^T}$

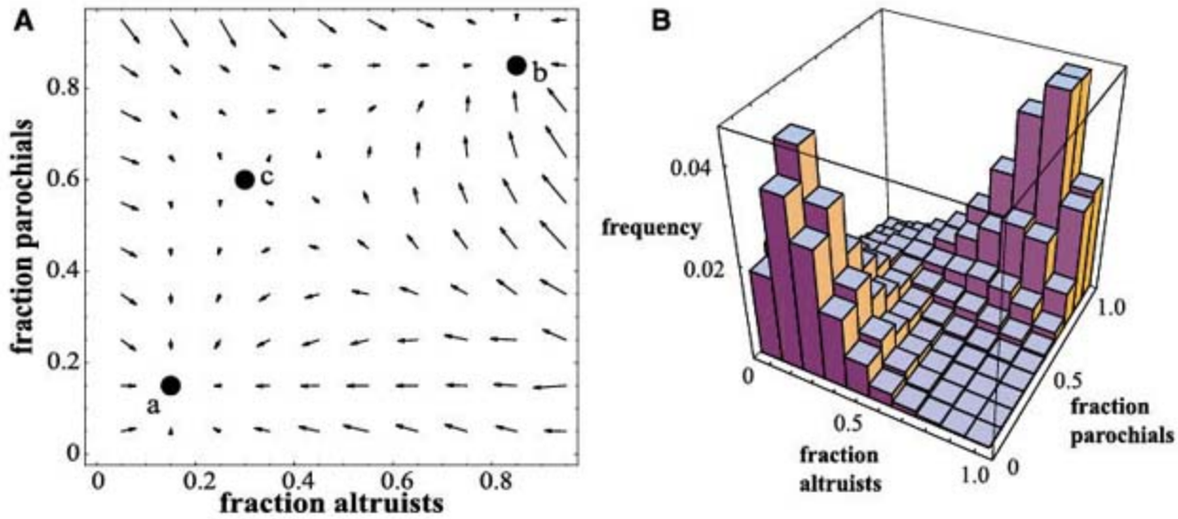

Fig. 2. Parochial altruist and tolerant nonaltruist outcomes occur with high frequency. The parameter values are as in Table 1 and Fig. 1. **(A)** Each vector represents the expected change at each state, based on a transition matrix recovered from the underlying perturbed Markov process on the basis of 5 million observations from 10 runs of 5000 generations starting at each of the 100 states as described in (*19*). Longer arrows reflect a higher net transition probability from each state. Stable states (i.e., states at which the population will spend the most time under the dynamic given by our model) occur where both frequencies are ~15% (point a) and both ~85% (point b). Point c is a saddle (unstable critical point). **(B)** The height of the bars gives the long run fraction of time in which we observe the indicated pair of population-level frequencies of altruists and parochials in the population.

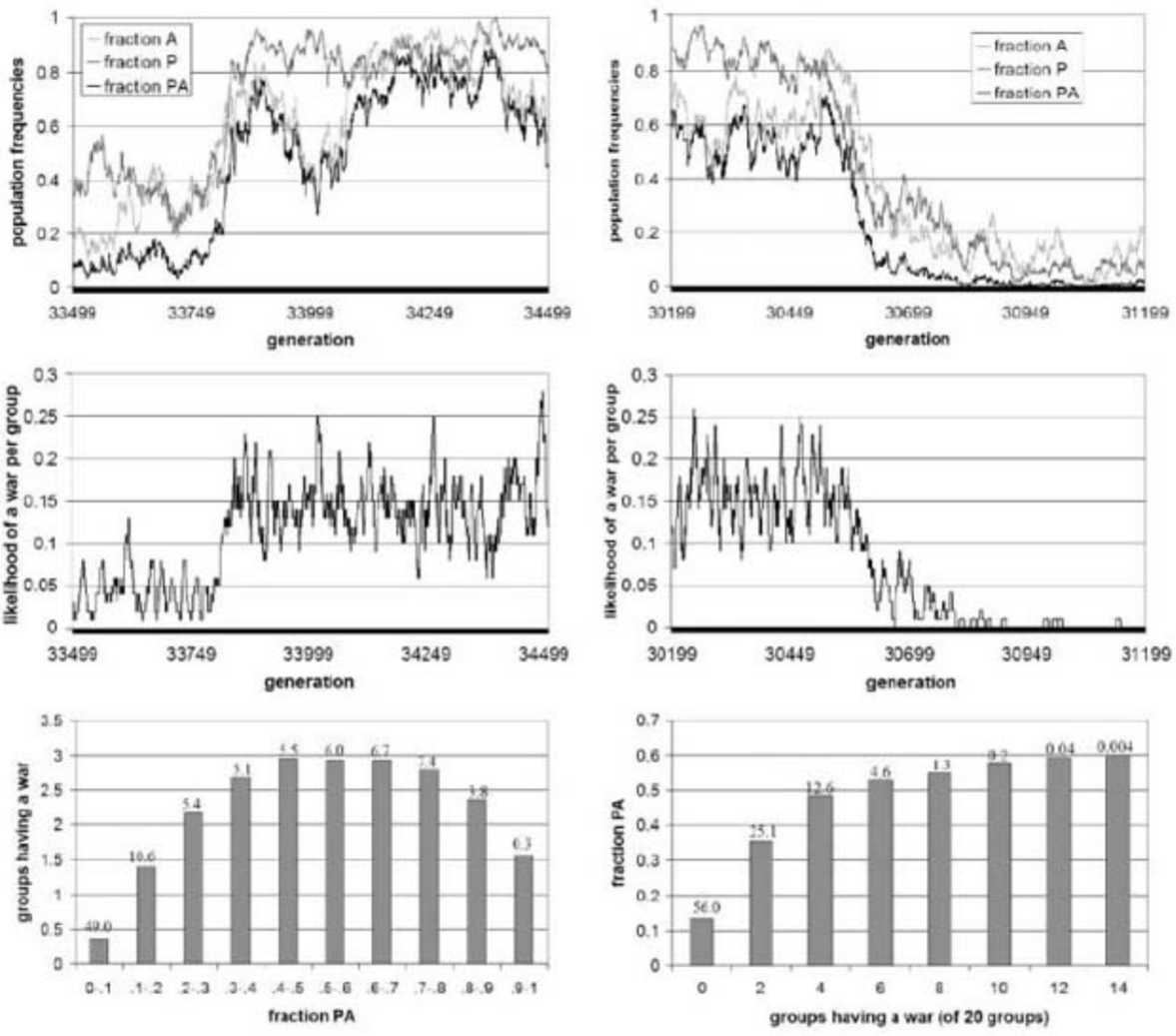

Fig. 3. Transitions between peace and war. The left panels in the top and the middle row illustrate a transition from a state near point a to one near point b in Fig. 2A. The right panels in the top and middle row show a reverse transition. Near point b in Fig. 2A, two-thirds of the population are PAs on average, and three-quarters of group interactions are hostile. Near point a, these figures are 4% and 24%, respectively. The bottom panels show that high frequencies of parochial altruists in the population sustain high frequencies of warfare and vice versa. Wars are most frequent when 40 to 70% of the population are parochial altruists (because at these frequencies imbalances between groups are more common). The numbers at the top of each bar indicate the percentage of 50,000 generations in which this fraction of PAs and this many wars occurred.

in our model exist, or that were they to exist they could be expressed in the complex behaviors involved in helping others and engaging in lethal conflict. Thus, we have not shown that a warlike genetic predisposition exists, only that should one exist, it might have coevolved with altruism and warfare in the way that we have described.

The vertical (parent-to-child) genetic transmission process in the model could be modified to encompass cultural learning processes and incorporate influences of peers and nonparental adults as well as parents. This extension would be essential if inferences about contemporary behavior are to be drawn from the model, for there is ample evidence that human parochialism can be readily redirected and even overridden by deliberate teaching, accidental exposure, and other aspects of socialization.

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Nanomechanical Basis of Selective Gating by the Nuclear Pore Complex

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The nuclear pore complex regulates cargo transport between the cytoplasm and the nucleus. We set out to correlate the governing biochemical interactions to the nanoscopic responses of the phenylalanine-glycine (FG)–rich nucleoporin domains, which are involved in attenuating or promoting cargo translocation. We found that binding interactions with the transport receptor karyopherin-β1 caused the FG domains of the human nucleoporin Nup153 to collapse into compact molecular conformations. This effect was reversed by the action of Ran guanosine triphosphate, which returned the FG domains into a polymer brush-like, entropic barrier conformation. Similar effects were observed in *Xenopus* oocyte nuclei in situ. Thus, the reversible collapse of the FG domains may play an important role in regulating nucleocytoplasmic transport.

Nuclear pore complexes (NPCs) regulate nucleocytoplasmic transport (NCT) across the nuclear envelope (*1*–*3*). Each vertebrate NPC is a ~120-MD supramolecular assembly comprising ~30 different proteins, known as nucleoporins, that surround a central pore ~40 nm in diameter (*4*). The nucleoporins that are implicated in NCT are generally located near the nuclear and cytoplasmic peripheries of the NPC (*5*) and consist of natively unfolded domains rich in Phe-Gly repeat motifs (i.e., FG domains) (*6*). FG domains exhibit a functional redundancy (*7*) in terms of their binding promiscuity to transport receptors known as karyopherins (Kaps; also called importins and exportins) (*8*), which are required to facilitate NCT of specific cargos greater than 40 kD in size (but smaller than the pore diameter) (*9*). In the absence of Kaps, the FG domains impose a physical barrier that impedes the passage of macromolecules through the NPC (*5*, *10*).

The dualistic functionality of the NPC, termed selective gating, is not strictly governed by size exclusion but exhibits a relative porosity that depends on the biochemical interactions involved during NCT. However, difficulties in directly visualizing the FG domains and their functional behavior in vivo (*4*) have allowed only figurative descriptions of Kap movement, such as "stepping from one FG-repeat to the next" (*11*), "sliding over oily spaghetti" (*12*), or "sliding over a surface comprised of FG-repeats" (*13*). Alternatively, the FG domains may resemble a gel-like "selective phase" within which only Kaps stay soluble and can "melt" through (*10*, *14*). Hence, the question remains as to how Kaps physically affect the FG domains to facilitate transport across the NPC.

To correlate the barrier-like behavior of the FG domains vis-à-vis Kaps, we covalently tethered the FxFG repeat–rich domain of Nup153 via terminal cysteines (i.e., Cys-hNup153-C or cNup153) to gold "nanodots" ~100 nm in diameter (*15*) (Fig. 1A). This allowed us to replicate a number of contextual details of the NPC: (i) FG-domain behavior in the NPC occurs at nanoscopic length scales; (ii) each FG domain is anchored at one end to the NPC while the other end dangles out into solution, rather than freely floating in solution; and (iii) a limited number of FG domains are confined to each NPC. Atomic force microscope (AFM) measurements provided the spatial distribution of the measured forces with respect to a cNup153-tethered nanodot (fig. S1). In the absence of karyopherin-β1 (Kapβ1, also called importin-β), the cNup153 molecules exhibited a long-range steric repulsive force (Fig. 1A), which indicated that they were in a polymer brush-like, entropic barrier conformation (*15*).

Changes in the response of cNup153 were obtained by monitoring the brush height L_{exp}, decreasing from 29.1 nm → 17.9 nm → 13.7 nm → 11.3 nm as the Kapβ1 concentration was increased from 0 → 115 fM → 2.5 pM → 33 nM, respectively (Fig. 1, A and B). This decrease in L_{exp} is comparable to the behavior observed in hexanediol (*15*) and indicates that the cNup153 molecules have transformed from a brush-like into

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a more collapsed, compact state. This behavior is also consistent with AFM single-molecule force spectroscopy measurements, which showed that Kapβ1-FG binding interactions cause individual cNup153 molecules to adopt more compact conformations that require a larger mechanical force (and work) to unfold (*16*).

Nuclear import is terminated by Ran guanosine triphosphate (RanGTP), which dissociates Kapβ1 from the FG domains and inhibits Kapβ1-FG binding in the nucleus (*11*). Thus, RanGTP should effectively reverse the collapse of the cNup153 molecules by sequestering Kapβ1. To test this hypothesis, we introduced incremental amounts of RanGTP (specifically, the GTPase-deficient mutant RanQ69L-GTP) into the buffer after the distended cNup153 molecules (L_{exp} = 33.7 ± 4.1 nm) were made to collapse in 0.33 nM Kapβ1 (L_{exp} = 7.4 ± 3.6 nm). As anticipated, L_{exp} increased from 7.4 ± 3.6 nm → 10.4 ± 3.7 nm → 16.2 ± 3.6 nm → 34.5 ± 6.4 nm upon increasing RanGTP from 0 → 0.1 nM → 0.2 nM → 0.56 nM, respectively (Fig. 2A). This result indicated that the entropic barrier was fully restored and confirmed that the collapse of cNup153 induced by Kapβ1-FG binding is reversible by the action of RanGTP.

As a negative control, the effect of Ran guanosine diphosphate (RanGDP; specifically, RanQ69L-GDP) was also tested on the cNup153 molecules. Unlike RanGTP, the association between RanGDP and Kapβ1 is negligible and does not affect the nuclear import of Kapβ1 (*17*). Additions of RanGDP (up to 40 nM) had no effect (L_{exp} = 10.9 ± 3.1 nm) on the cNup153 molecules, which were made to collapse in 33 nM Kapβ1 (L_{exp} = 12.4 ± 3.9 nm). Nonetheless, a subsequent injection of 35 nM RanGTP effectively reversed the collapsed state of the cNup153 molecules (L_{exp} = 28.0 ± 5.7 nm; Fig. 2B).

Nup153 has one of the few FG domains (Nup153-C) that has been topologically mapped using domain-specific antibodies (*18*). Hence, its anchoring site at the distal ring of the NPC (*18*) allowed us to monitor its distribution at different functional states within the NPC. We used immunogold electron microscopy to establish a direct topological correlation to the collapse of Nup153-C in the NPC. At steady state, Nup153-C appeared diffuse around the nuclear basket of the NPC (Fig. 3, A and D) (*18*). Consequently, a microinjection of 2 μM Kapβ1 produced a striking phenotype that was localized around the distal ring (Fig. 3, B and E), consistent with the collapse of the Nup153-C FG domains toward their anchoring sites. A further microinjection of 8 μM RanGTP then returned the Nup153-C to its steady-state distribution (Fig. 3, C and F). In comparison, the collapse of Nup153-C was not reversible with 8 μM RanGDP as the second microinjection (fig. S2 and table S1).

The noncohesive properties of the FxFG domains (*19*) suggest that their reversible collapse may play a prominent role in the selective gating of the NPC, particularly in vertebrate NPCs, which almost exclusively consist of FxFG domains (except for the GLFG domain of Nup98) (*2*). As we conceptualize in Fig. 3G, selective gating consists of a rapid, stochastic flux of collapsing and distending FG domains owing to the dynamic nature of NCT, rather than switching only between "open" (i.e., collapsed) or "closed" (i.e., entropic barrier) states. Because the rate of NCT is much slower than the relaxation time of a random polypeptide coil (millisecond versus microsecond time scales) (*20*), this may explain the increased transport rates at elevated Kapβ1 concentrations (*21*). This view is further supported by the fact that the FG domains (in the midst of ongoing Kap-FG interactions) are not phenotypically collapsed, as additional nonphysiological reagents (i.e., hexanediol) are required to abolish the NPC barrier altogether (*10*, *22*).

To breach the entropic barrier, Kap-FG binding interactions cause the participating FG domain(s) to collapse locally toward their anchoring sites in the NPC, effectively "reeling" Kap-cargo complexes into the central pore as the FG domains bind to multiple hydrophobic sites on the Kap (*23*) [e.g., via "fly-casting" (*24*)]. It is noteworthy that the reversible collapse of the FG domains can also accommodate large-scale rearrangements within the central pore during the translocation of larger objects [e.g., viruses (*9*)]. Taken together with the collapse of Nup153 in hexanediol (*15*) and at 4°C (*25*), such behavior substantiates the notion that natively unfolded proteins can function between extended-disordered and collapsed-disordered states as a result of changes in their configurational entropy (*26*). Nonetheless, the quantitative extent of the FG-domain collapse during physiological NPC function is difficult to predict in a cellular background of competing specific and nonspecific interactions (*27*, *28*).

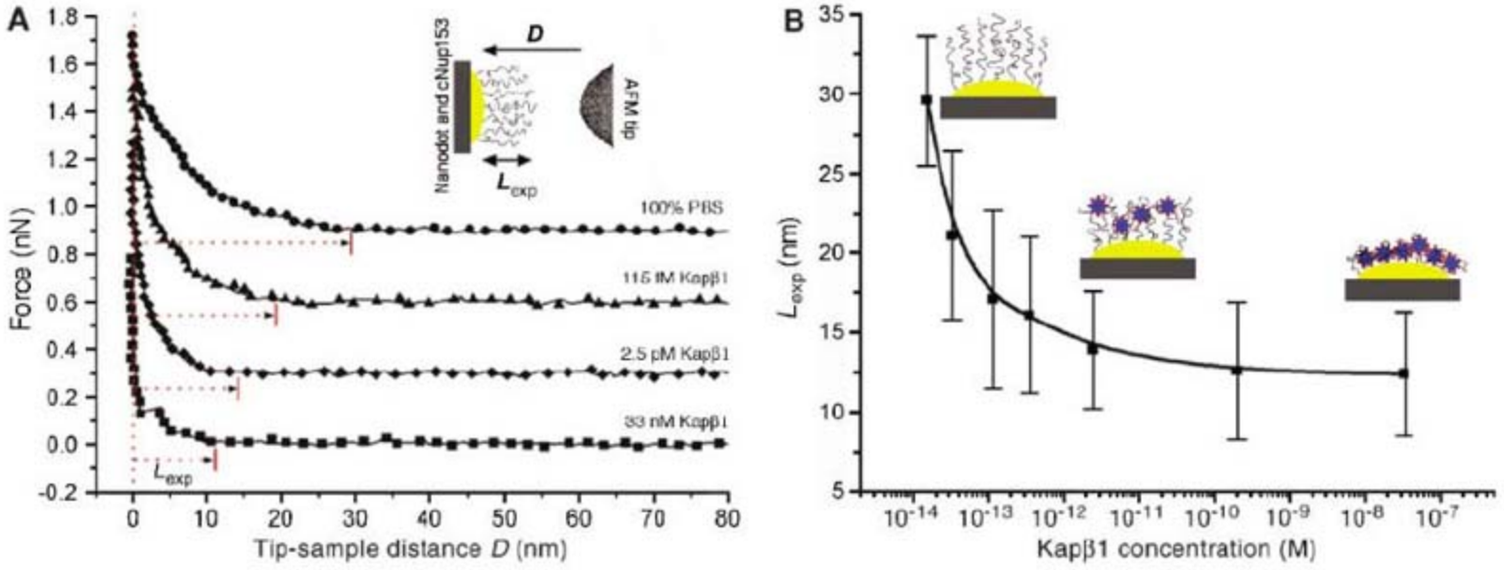

Fig. 1. Kapβ1-FG interaction drives the collapse of cNup153. (**A**) The onset of steric repulsion measured by an approaching AFM tip (over a tip-sample distance *D*) provides a measure of the spatial range of the nanodot-tethered cNup153 molecules (L_{exp}). Representative measurements show that L_{exp} decreases from 29.1 nm → 17.9 nm → 13.7 nm → 11.3 nm as the Kapβ1 concentration is increased from 0 (100% phosphate-buffered saline) → 115 fM → 2.5 pM → 33 nM, respectively. Each force curve is offset by 0.3 nN to aid visual clarity. (**B**) The decay of L_{exp} with increasing concentrations of Kapβ1 indicates that the collapse of cNup153 is caused by Kapβ1-FG binding; as illustrated, eight FG-binding "hydrophobic patches" (red) are included on individual Kapβ1 molecules (blue). This highlights how multiple binding interactions may occur between Kapβ1 and neighboring cNup153 molecules. L_{exp} does not reduce to zero because Kapβ1 is incorporated into the collapsed cNup153 molecules. Each data point corresponds to an average value of L_{exp} obtained over ~100 force curves at the given Kapβ1 concentration. Error bars denote SD.

We have been able to reconcile the dualistic nature of selective gating within the context of FG-domain behavior by correlating the biophysical responses of the Nup153 FG domain to the biochemical interactions that govern NCT. The ability to resolve the nanoscopic behavior of the FG domains by identifying more closely the contextual details of the NPC highlights differences with macroscopic views [e.g., FG-hydrogel (*14*)] that deserve consideration (supporting online text). At such nanometer length scales, the increase in surface-to-volume ratio implies that interfacial effects such as the brush-like behavior of the FG domains may become increasingly dominant (*29*). Thus, other physical attributes, such as the distance between the FG domains with respect to their anchoring sites relative to the pore topography, may also be important in determining how selective gating is optimized in the NPC. Another question concerns the hysteresis arising from the conformational sensitivity of the FG domains to Kaps and other conditions (e.g., pH and temperature) and whether such "memory effects" can bias their behavior during experimentation. For now, the reversible collapse provides a useful benchmark in quantifying the behavior of FG domains, as well as a means to identify their respective anchoring sites in the NPC. More generally, the reversible collapse of (bio)polymers may be applied toward the selective gating of molecular transport and sieving processes in diverse applications unrelated to NCT.

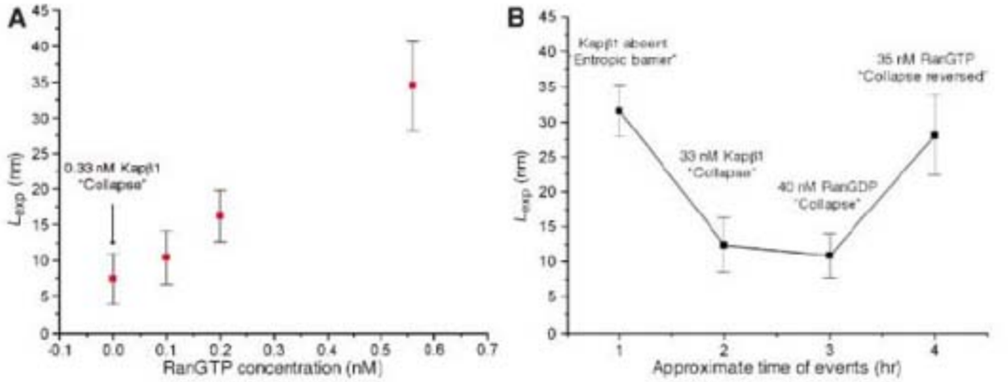

Fig. 2. cNup153 collapse induced by Kapβ1-FG binding is reversible by RanGTP. (**A**) After a collapse of cNup153 in 0.33 nM Kapβ1, L_{exp} increases from 7.4 ± 3.6 nm → 10.4 ± 3.7 nm → 16.2 ± 3.6 nm → 34.5 ± 6.4 nm as RanGTP is increased from 0 → 0.1 nM → 0.2 nM → 0.56 nM. The initial value of L_{exp} before collapse was 33.7 ± 4.1 nm, hence the cNup153 collapse is completely reversed in 0.56 nM RanGTP. (**B**) Sequential additions of Kapβ1, RanGDP, and RanGTP demonstrate how the reversible collapse is regulated. Starting with the requisite cNup153 brush-like conformation (L_{exp} = 31.6 ± 3.7 nm), injection of 33 nM Kapβ1 causes the barrier to collapse (L_{exp} = 12.4 ± 3.9 nm). A subsequent addition of 40 nM RanGDP has no effect on reversing its collapse (L_{exp} = 10.9 ± 3.1 nm). However, an additional 35 nM RanGTP effectively reverses the collapsed state of the cNup153 molecules (L_{exp} = 28.0 ± 5.7 nm). Each data point corresponds to an average value of L_{exp} obtained over ~100 force curves at each respective condition. Error bars denote SD.

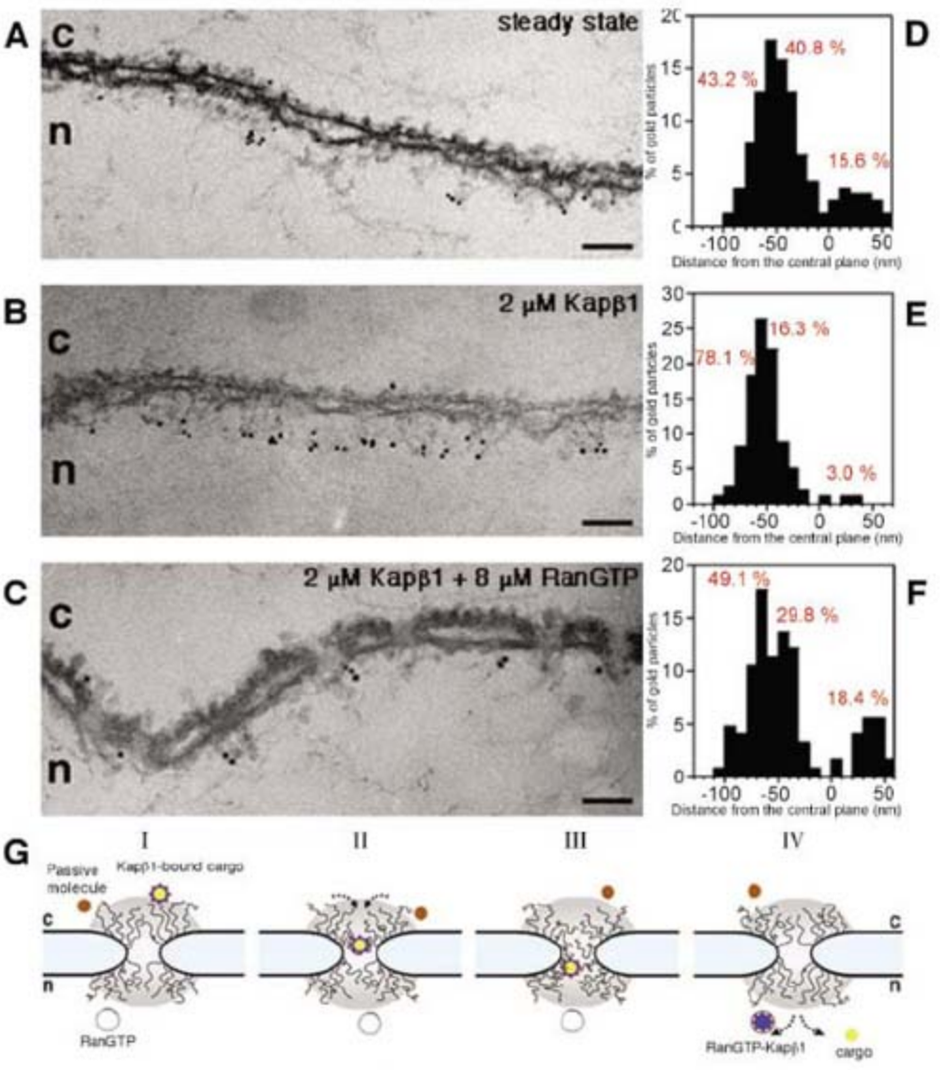

Fig. 3. Reversible collapse of Nup153-C in the NPC revealed by immunogold electron microscopy. (**A**) Nup153-C is diffuse within the nuclear periphery of the NPC at steady state. (**B**) After a microinjection of 2 μM Kapβ1 into the cytoplasm, Nup153-C is located predominantly at the distal ring of the NPC, indicating a collapse of Nup153-C to its anchoring site. (**C**) An additional microinjection of 8 μM RanGTP reverses the Kapβ1-induced collapse by returning Nup153-C to its steady-state distribution. These observations are summarized in the histograms, where 0 nm in the *x* axis corresponds to the central plane of the NPC, and the distal ring, nuclear ring, and cytoplasmic ring moieties are located at –100 nm to –50 nm, –50 nm to 0 nm, and 0 nm to 60 nm, respectively. (**D**) Steady state (n = 164). (**E**) 2 μM Kapβ1 (n = 159). (**F**) 2 μM Kapβ1 + 8 μM RanGTP (n = 124). (**G**) Model of selective gating based on the reversible collapse of the FG domains. I: The FG domains form a corona-like entropic barrier surrounding the NPC in the absence of Kapβ1-FG binding interactions. The gray shaded area emphasizes (i) the range of the entropic barrier, and (ii) the stochastic fluctuations of the FG domains. II: Kap-FG binding causes a local collapse of the participating FG domains toward their anchoring sites, thereby drawing the Kap-cargo complex into the central pore. III: Kap-cargo complexes translocate stochastically to the nuclear periphery via a flux of binding-collapsing and unbinding-distending processes. IV: RanGTP biases the direction of transport into the nucleus by sequestering the Kap, which dissociates the cargo and prevents further Kap-FG interaction. Throughout, non–Kap-bound FG domains maintain the entropic barrier in order to exclude passive molecules from the NPC near-field. The cytoplasmic filaments and the nuclear basket have been omitted to emphasize the generality of selective gating. Scale bars in (A) to (C), 100 nm; c, cytoplasm; n, nucleus.

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Changes in Regulation of a Transcription Factor Lead to Autogamy in Cultivated Tomatoes

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We report the cloning of *Style2.1*, the major quantitative trait locus responsible for a key floral attribute (style length) associated with the evolution of self-pollination in cultivated tomatoes. The gene encodes a putative transcription factor that regulates cell elongation in developing styles. The transition from cross-pollination to self-pollination was accompanied, not by a change in the STYLE2.1 protein, but rather by a mutation in the *Style2.1* promoter that results in a down-regulation of *Style2.1* expression during flower development.

The ability of plants to evolve new mating behaviors is a notable feature of plant evolution. The most common change is for obligate cross-pollinating (allogamous) species to give rise to self-pollinating (autogamous) species, and it is estimated that 20 to 50% of all extant plant species (including many cultivated plants) are autogamous (*1*–*3*). Research suggests that the first step in the evolution of autogamy from obligate allogamy is the mutational loss of self-incompatibility, the molecular bases of which are now well understood (*4*). However, loss of self-incompatibility is not sufficient to guarantee self-fertilization. Changes in floral morphology are also required to promote self-pollination rather than cross-pollination; however, the molecular bases of these changes have been hitherto unknown (*5*, *6*).

A change in the position of the pollen-bearing anthers relative to the stigmatic surface of the pistil is commonly associated with the evolution of autogamy. Flowers in which the stigma is exserted beyond its own anthers are more likely to receive pollen from neighboring plants (Fig. 1, B and D), whereas flowers in which the stigma is recessed relative to its own anthers (Fig. 1, A and C) are more likely to self-pollinate. Nowhere is this better exemplified than in the evolution of the cultivated tomato, *Solanum lycopersicum*. Most wild tomato species are allogamous and bear flowers with highly exserted stigmas (Fig. 1, B and D) (*7*, *8*). However, the cultivated tomato is autogamous and normally bears flowers with recessed stigmas (Fig. 1, A and C). Fortunately, *S. lycopersicum* readily forms fertile interspecific hybrids with most of its allogamous wild relatives, which permits the use of genetics to dissect the basis of the changes in floral structure that accompanied the evolution of the autogamous cultivated tomato from an ancestral state of allogamy (*9*–*12*).

Recently, a series of quantitative trait locus (QTL) mapping experiments, using interspecific crosses between *S. lycopersicum* and various wild, allogamous species, have revealed that a single major QTL on chromosome 2 accounts for most of the structural changes that attended the evolutionary transition from allogamous flowers to autogamous flowers (*10*, *11*). This QTL, designated *stigma exsertion 2.1* or *se2.1*, was subsequently shown to be a complex locus composed of at least five closely linked genes: three controlling stamen length, one controlling style length, and one conditioning anther dehiscence (*12*) (Fig. 2, A and B). Of these five loci, the one controlling style length (designated *Style 2.1*) accounts for the greatest

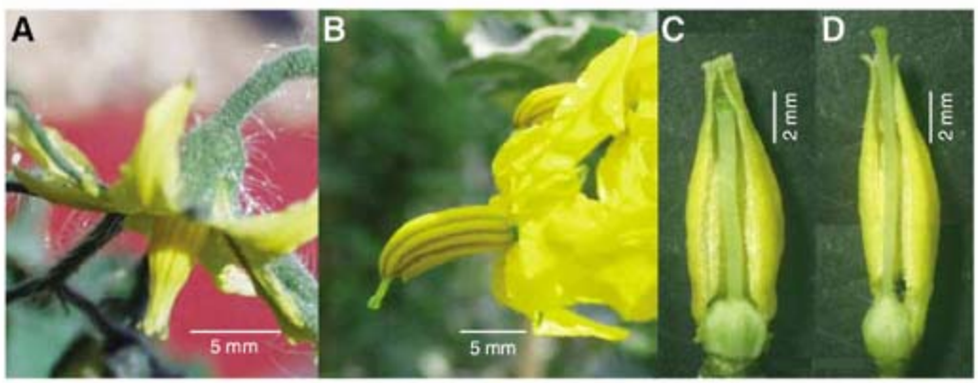

Fig. 1. (**A**) Flower from self-pollinating cultivated tomato (*S. lycopersicum*). (**B**) Flower from outcrossing, wild species *S. pennellii*. The stigma surface is recessed relative to the anther cone in *S. lycopersicum* but exserted in *S. pennellii*. (**C**) Cross section of flower from *S. lycopersicum* NIL with short-style allele (recessed stigma). (**D**) Cross section of flower from *S. lycopersicum* NIL with long-style allele (exserted stigma).

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change in stigma exsertion and was hence selected for further study (*12*).

To identify the segment of DNA containing the *Style2.1* locus, a high-resolution map was created using 2704 F2 individuals derived from a cross between the cultivated tomato M82 and a nearly isogenic line IL2-5, which carry the "short-style" and "long-style" alleles at the *Style2.1* locus, respectively (*12*). The long-style allele derived from selective introgression from the wild, allogamous species *S. pennellii* (Fig. 1B). The cause of style length variation was delineated between two adjacent crossover events (TA3043 and TA3034) encompassing a 20-kb interval in a previously described *S. lycopersicum* bacteria artificial chromosome (BAC) clone (Fig. 2, C and D) (*12*). Annotation of the BAC revealed a single predicted gene in the 20-kb interval, designated *L04*, as well as the 5′ promoter region for a second gene, designated *L02* (Fig. 2D).

In an effort to determine whether *L02* or *L04* are causally related to the short-style and long-style phenotypes, we executed a series of plant transformation experiments. Individual constructs containing the entirety of the *L04* and *L02* coding regions, as well as upstream and downstream regions (fig. S1), from a long-style, nearly isogenic line (NIL) (long-style genotype), were transformed into a short-style NIL (short-style genotype). The long-style allele is known to be dominant over the short-style allele (*12*); hence, transformation of the long-style *Style 2.1* allele into a short-style genotype would be expected to yield plants with longer styles. A total of 22 independent *L04* transformants were analyzed and compared with seven control plants transformed with only the *L04* promoter (table S1, A and B). Statistical tests determined that the *L04* transformants did not produce flowers with styles significantly longer than the controls ($P = 0.49$) (table S1A). In contrast, 11 independent *L02* transformants developed flowers with significantly elongated styles relative to eight control plants transformed with only the *L02* promoter ($P = 0.01$) (table S1, C and D). These results were also verified in the subsequent T_1 generation for selected T_0 plants (table S1, E and F, and fig. S2). Further, *L02* was also transformed into tobacco, and again resulted in transformants with significantly elongated styles ($P = 0.03$) (table S1, I and J).

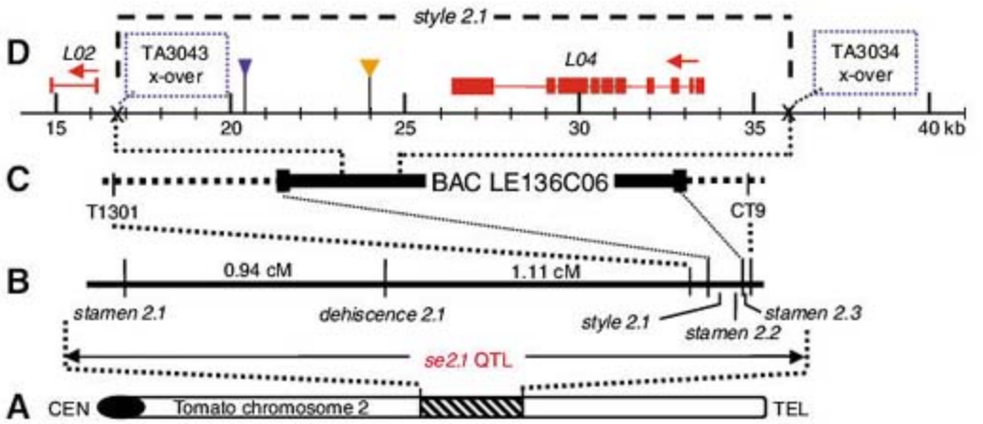
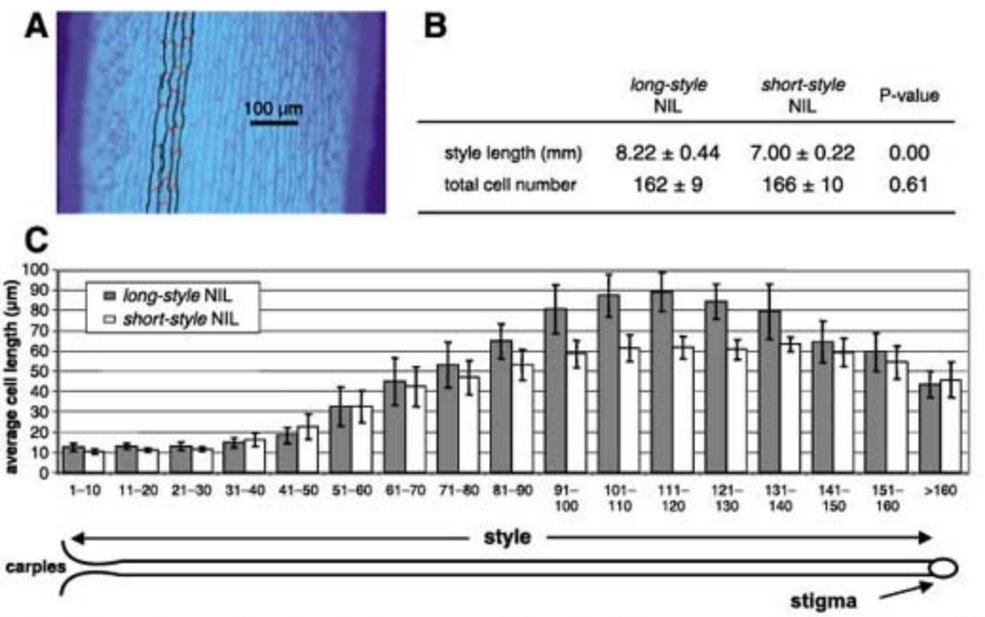


Fig. 2. High-resolution mapping of *se2.1* QTL. **(A)** Position of *se2.1* on tomato chromosome 2. **(B)** Genetic dissection of the *se2.1* QTL into five separate component loci, including *style2.1*. **(C and D)** Key crossover events (TA3034 and TA3043) delineating the *style2.1* locus to a 20-kb segment of BAC clone LE136C06. Blue and gold reverse triangles show positions of 450-bp and 750-bp indels, respectively.



	long-style NIL	short-style NIL	P-value
style length (mm)	8.22 ± 0.44	7.00 ± 0.22	0.00
total cell number	162 ± 9	166 ± 10	0.61

Fig. 3. Cell number and cell length of mature styles from both long-style and short-style NILs. **(A)** Florescent image of style used to measure cell length and cell number. The four black vertical lines superimposed on the image demarcate the three adjacent cell files measured. The red horizontal lines indicate the boundaries between cells. **(B)** Style length and cell number values presented as means ± 1.96 SEs. **(C)** The cell length averaged from consecutive sectors of 10 cells along the longitudinal axis of the style. Error bars, 95% confidence interval; filled bars, long-style NIL; hollow bars, short-style NIL.

These data all point to *L02* as the gene responsible for the *Style 2.1* QTL. Further, because only the 5′ region of *L02* is contained within the crossover interval that delineates the *Style 2.1* QTL, the cause of the QTL responsible for stigma exsertion, and thus cross-pollination, is predicted to reside in the regulatory region of the *L02* gene (Fig. 2D). To investigate this possibility, we generated two additional transformation constructs: (i) the promoter from the long-style *L02* allele fused with the coding region (cDNA) of the *L02* gene (long-style and short-style *L02* alleles encode identical proteins); (ii) the promoter from the short-style *L02* gene fused with the coding region (cDNA) of the *L02* gene. If the cause of the *Style 2.1* QTL resides in the *L02* promoter, one would predict that plants transformed with construct (i) should produce longer styles than those transformed with construct (ii). Transformation results bear out this prediction ($P < 0.01$) (table S1, G and H). We thus conclude that natural genetic variation in the *L02* promoter is responsible for the *Style 2.1* QTL and evolution from allogamy to autogamy in the cultivated tomato.

L02 encodes a short 92 amino acid polypeptide that bears a conserved helix-loop-helix (HLH) motif but lacks the basic region typical of the broad class of basic helix-loop-helix (bHLH) proteins (fig. S3). The HLH motif is known to mediate protein-protein interactions among bHLH proteins that function as transcription factors (*13*). Phylogenetic analysis revealed a few *L02* homologs in related solanaceous species, as well as *Arabidopsis* and rice (fig. S4). Five of the *Arabidopsis* homologs (At5g39860, At5g15160, At1g74500, At3g47710, and At3g28857) have been shown to enhance hypocotyl length when each individual gene was constitutively expressed (*14*).

The two *Style 2.1* NILs were subjected to developmental and in situ hybridization studies in an effort to determine in which tissues and

stages of flower development *L02* is expressed. The results indicate that *L02* RNA is present throughout style development (fig. S5A). Moreover, while *L02* is mainly expressed in developing stylar tissue, some expression can also be observed around the ovules (fig. S5, B to E). Further, the long-style NIL differs from the short-style NIL in that the former accumulates greater quantities of the *L02* transcript throughout style development (fig. S5A), a finding consistent with the prediction that the *Style 2.1* QTL is attributable to mutations in the 5′ regulatory portion of the *L02* gene rather than to changes in the amino acid sequence of the encoded protein.

In an effort to shed light on the mechanism by which *L02* modulates style elongation, we recorded cell number and size along the entire length of mature styles from both short-style and long-style genotypes (Fig. 3, A to C). Although the two genotypes differed significantly in style length, they did not differ with regard to the total number of cells in the long axis of each style, which suggests that increased cell elongation is responsible for the longer style length of the long-style genotypes (Fig. 3B). To investigate this hypothesis, each cell file along the longitude of individual styles was divided into consecutive sectors of 10 cells and measured (Fig. 3C). The average cell length of the two genotypes did not differ, except for the sector encompassing the 91st to 130th cells. In this distal region, cells of the long-style genotypes were significantly longer ($P < 0.01$) than their counterparts in the short-style genotypes (Fig. 3C). Thus, allelic variation at the *L02* gene modulates style length, and hence stigma exsertion, through localized, differential cell elongation in developing styles. These results also suggest that *L02* is a positive regulator of cell elongation, because greater accumulation of the *L02* transcript (as seen in the long-style genotype) is associated with greater cell elongation and hence with exserted styles.

The nucleotide sequence of the 5′ promoter region of *L02* (contained within the crossover interval that delimits the *Style2.1* QTL) (Fig. 2D and fig. S6) was compared between the long-style allele and the short-style allele. The results revealed a number of sequence differences, including 450-bp (base pair) and 750-bp deletions that were 4 kb and 8 kb upstream from the *L02* start codon, respectively (fig. S7). Sequence analysis from a broader cross section of tomato species revealed that only the 450-bp deletion is specific to the short-style allele found in the cultivated tomato and hence is a candidate for the cause of the down-regulation of *L02* associated with short styles (table S2). However, we cannot rule out the possibility that other, more subtle, sequence changes in the 5′ region of the *L02* promoter may be causal to the down-regulation of *L02* expression associated with the transition from long to short styles.

The evolution from allogamy to autogamy in plants is often associated with both a loss of self-incompatibility (mutation of the *S* locus) and a loss or reduction in stigma exsertion. Which occurs first is a matter of conjecture, but one would predict that self-incompatibility would be lost first (rendering the plants capable of self-pollination), followed by loss or reduction of stigma exsertion (making it more likely that the plants would automatically self-pollinate). If the loss of stigma exsertion occurred before the loss of self-incompatibility, the plants would be unable to either cross-pollinate or self-pollinate—a selective disadvantage. Examination of the phylogenetic tree of tomato and its wild relatives, with regard to mutations in the self-incompatibility (*S*) locus and short-style allele of *L02*, supports the previous order of events. Self-incompatibility was lost in the branch leading to the clade of five self-compatible species (fig. S8). However, the short-style allele of *L02* apparently occurred later in the branch of the phylogenetic tree leading to the cultivated tomato (fig. S8 and table S2). However, it must be recognized that this conjecture is based on genetic studies and sequencing on a relatively small subset of tomato species accessions. A fuller understanding of the evolution of the *Style 2.1* gene throughout the clade of tomato species must await further studies.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5850/643/DC1
Materials and Methods
Figs. S1 to S8
Tables S1 to S4
References and Notes

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Plant Pathogen Recognition Mediated by Promoter Activation of the Pepper *Bs3* Resistance Gene

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Plant disease resistance (R) proteins recognize matching pathogen avirulence proteins. Alleles of the pepper *R* gene *Bs3* mediate recognition of the *Xanthomonas campestris* pv. *vesicatoria* (*Xcv*) type III effector protein AvrBs3 and its deletion derivative AvrBs3Δrep16. Pepper *Bs3* and its allelic variant *Bs3-E* encode flavin monooxygenases with a previously unknown structure and are transcriptionally activated by the *Xcv* effector proteins AvrBs3 and AvrBs3Δrep16, respectively. We found that recognition specificity resides in the *Bs3* and *Bs3-E* promoters and is determined by binding of AvrBs3 or AvrBs3Δrep16 to a defined promoter region. Our data suggest a recognition mechanism in which the Avr protein binds and activates the promoter of the cognate *R* gene.

Resistance (R) proteins, a class of plant immune receptors that mediate recognition of pathogen-derived avirulence (Avr) proteins, are a well-studied facet of the plant defense system (*1*). The bacterial plant pathogen *Xanthomonas campestris* pv. *vesicatoria* (*Xcv*) uses a type III secretion (T3S) system to inject an arsenal of about 20 effector proteins into the host cytoplasm that collectively promote virulence (*2*). R protein–mediated defense in response to *Xcv* effector proteins is typically accompanied by a programmed cell death response referred to as the hypersensitive response (HR).

One Avr protein that R proteins recognize is AvrBs3, a member of a *Xanthomonas* family of highly conserved proteins (*3*). The central region of AvrBs3 consists of 17.5 tandem near-perfect

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34–amino acid repeat units that determine avirulence specificity (*4*). AvrBs3 also contains nuclear localization signals (NLSs) and an acidic transcriptional activation domain (AD) (*5*, *6*), similar to eukaryotic transcription factors, and induces host gene transcription (*7*). Mutations in the NLS or AD of AvrBs3 abolish pathogen recognition by the matching pepper *R* gene *Bs3* (*5*, *8*), which suggests that recognition involves the transcriptional activation of host genes.

Previously we identified bacterial artificial chromosome (BAC) clones derived from the pepper (*Capsicum annuum*) cultivar Early California Wonder 30R (ECW-30R) that cover the *Bs3* gene (*9*). For complementation-based identification, fragments of a *Bs3*-containing BAC (*9*) were cloned into a plant transformation vector and were delivered into *Nicotiana benthamiana* leaves via *Agrobacterium tumefaciens*–mediated transient transformation. Two nonidentical clones carrying the same coding sequence triggered an HR in *N. benthamiana* when cotransformed with *avrBs3*. A genomic DNA fragment containing only the predicted coding sequence and ~1 kb of sequence upstream of the ATG mediated AvrBs3 recognition, confirming that this gene is *Bs3* (Fig. 1A).

AvrBs3 mutants lacking the AD (AvrBs3ΔAD) or repeat units 11 to 14 (AvrBs3Δrep16) did not trigger HR in pepper *Bs3* plants (*4*, *5*) and also failed to trigger HR in *N. benthamiana* when coexpressed with the cloned *Bs3* gene (Fig. 1A). AvrBs4, which is 97% identical to AvrBs3 but is not recognized by pepper *Bs3* genotypes (*10*), also did not trigger HR in *N. benthamiana* when coexpressed with *Bs3* (Fig. 1A). Therefore, *Bs3* mediates specific recognition of wild-type AvrBs3 in both pepper and *N. benthamiana*, but not when AvrBs3 lacks the AD or repeat units 11 to 14; nor does *Bs3* mediate recognition of the AvrBs3-like AvrBs4 protein (Fig. 1C).

The *Bs3* gene has three exons and two introns (Fig. 1D), is 342 amino acids long (fig. S1), and is homologous to flavin-dependent mono-

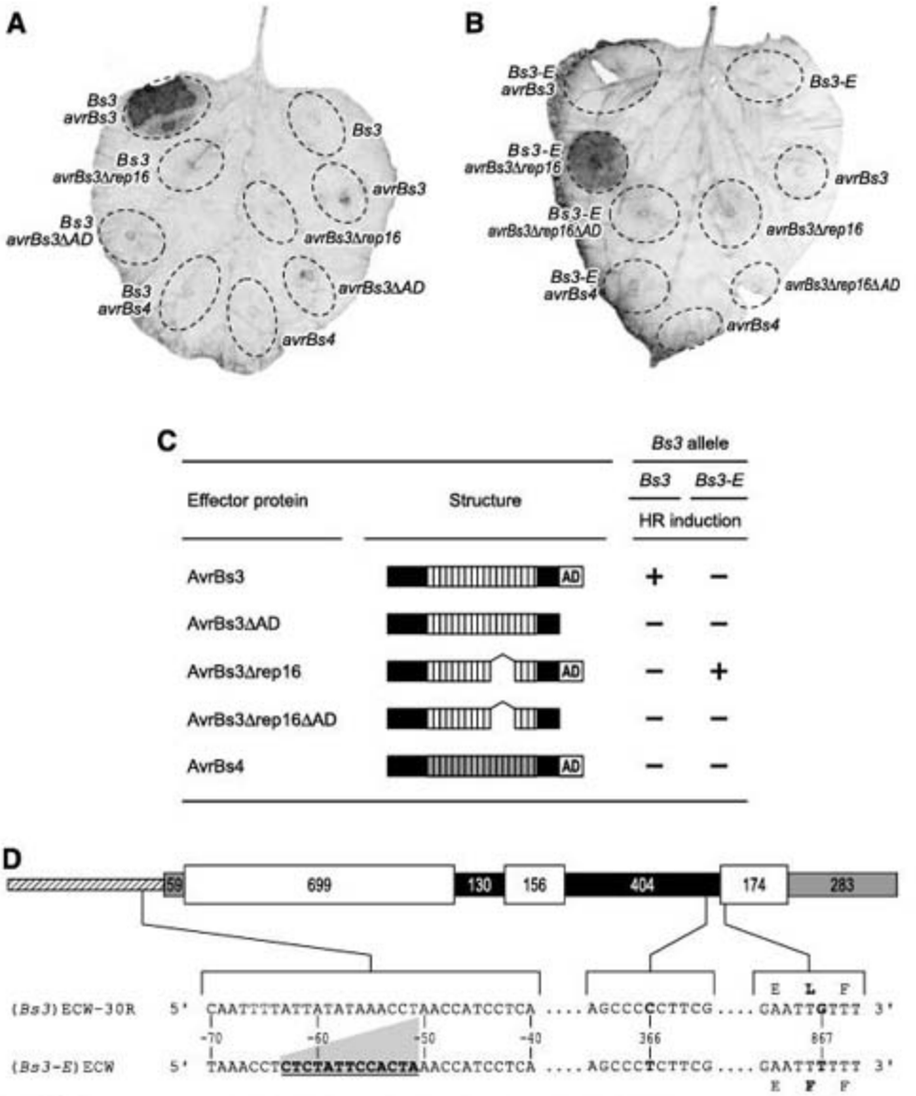

Fig. 1. (**A**) Recognition specificity of the *Bs3* allele from ECW-30R. The *Bs3* gene and/or *avr* genes were expressed transiently in *N. benthamiana* leaves via *A. tumefaciens* (OD_{600} = 0.8). Dashed lines mark the inoculated areas. Four days after infiltration, the leaves were cleared to visualize the HR (dark areas). (**B**) *Bs3-E* and/or *avr* genes were transiently expressed in *N. benthamiana* leaves. (**C**) The relationship between domain structure and activity of AvrBs3, AvrBs3 derivatives, and AvrBs4. Plus and minus signs indicate presence or absence of the HR in *N. benthamiana* upon coexpression of the pepper *Bs3* or *Bs3-E* allele, respectively. For details, see Fig. 1A. White- and gray-boxed areas in the central part of the protein represent the repeat region of AvrBs3 and AvrBs4, respectively. AD refers to the C-terminal acidic transcriptional activation domain. (**D**) Gene structure of the ECW-30R *Bs3* and the ECW *Bs3-E* alleles. Exons, introns, untranslated regions, and promoter regions are displayed to scale as white, black, gray, and hatched boxes, respectively. The length of these elements (in base pairs) is indicated within the boxes. Differences between the *Bs3* alleles are marked in boldface. A 13-bp insertion in the *Bs3-E* promoter relative to the *Bs3* promoter is underlined. Nucleotide positions of the promoter and exon 3 polymorphisms are relative to the transcriptional and translational start sites, respectively. Amino acids encoded by the polymorphic region in exon 3 (E, Glu; L, Leu; F, Phe) are depicted above and below the nucleotide sequences.

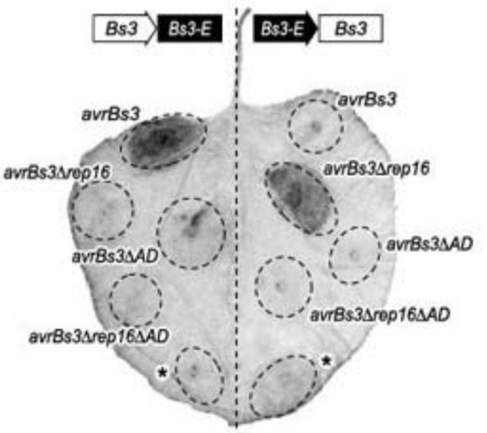

Fig. 2. Chimeras containing the promoter (arrow) of the *Bs3* allele (white) and the coding region (box) of the *Bs3-E* allele (black) or the reciprocal combination (right side of the leaf) were expressed together with *avrBs3*, *avrBs3Δrep16*, and derivatives as indicated. Asterisks mark areas in which only *A. tumefaciens* delivering the chimeric constructs was infiltrated. Dashed lines mark the inoculated areas. Four days after inoculation, leaves were cleared to visualize the HR (dark areas).

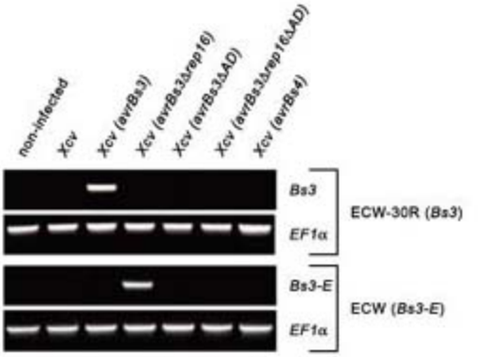

Fig. 3. Semiquantitative RT-PCR on cDNA of non-infected and *Xcv*-infected pepper ECW-30R (*Bs3*) and ECW (*Bs3-E*) leaves 24 hours after infection. The *avrBs3*-like genes that are expressed in the given *Xcv* strains are indicated in parentheses. Elongation factor 1α (EF1α) was amplified as a control.

oxygenases (FMOs) (fig. S2) (*11*). Bs3 is most closely related to FMOs of the *Arabidopsis* YUCCA family (fig. S3) but lacks a stretch of ~70 amino acids present in all related FMOs (fig. S4).

The AvrBs3 derivative AvrBs3Δrep16, which lacks repeat units 11 to 14, triggers HR in the pepper cultivar ECW but not in the near-isogenic *Bs3*-resistant cultivar ECW-30R (*4*). We transformed *N. benthamiana* with the ECW *Bs3* allele (termed *Bs3-E*) including ~1 kb of the promoter and showed that it mediated recognition of AvrBs3Δrep16 but not AvrBs3 (Fig. 1B). Furthermore, AvrBs3Δrep16 lacking the C-terminal AD did not trigger HR when coexpressed with *Bs3-E* (Fig. 1B), and *Bs3-E* did not mediate recognition of AvrBs4. Thus, *Bs3* and *Bs3-E* represent functional alleles with distinct recognition specificities (Fig. 1C). The coding sequences of the two *Bs3* alleles differ by a single nucleotide conferring a nonsynonymous change in exon 3, resulting in a leucine-phenylalanine difference (Fig. 1D and fig. S1). The promoter regions also differed by a 13–base pair (bp) insertion in *Bs3-E* compared to *Bs3*, at position –50 relative to the transcription start site.

We fused the *Bs3* promoter to the *Bs3-E* coding sequence and vice versa, then cotransformed *N. benthamiana* with these chimeras in combination with *avrBs3*, *avrBs3Δrep16*, or the corresponding AD mutant derivatives. The *Bs3* promoter fused to the *Bs3-E* coding sequence mediated exclusively AvrBs3 recognition, whereas the reciprocal chimera (*Bs3-E* promoter fused to the *Bs3* coding sequence) mediated exclusively recognition of AvrBs3Δrep16 (Fig. 2). Thus, the promoter and not the coding region determines recognition specificity of the pepper *Bs3* alleles.

Semiquantitative reverse transcription polymerase chain reaction (RT-PCR) revealed strongly increased *Bs3* transcript levels in pepper ECW-30R *Bs3* plants upon infection with *avrBs3*-expressing, but not *avrBs3Δrep16*- or *avrBs4*-expressing, *Xcv* strains (Fig. 3). Likewise, *Bs3-E* levels in ECW *Bs3-E* plants increased upon infection with *avrBs3Δrep16*-expressing *Xcv* strains, but not when infected with *avrBs3*- or *avrBs4*-expressing *Xcv* strains. AD-mutant derivatives of *avrBs3* and *avrBs3Δrep16* did not induce accumulation of *Bs3* or *Bs3-E* mRNA. Expression patterns were unaltered in the presence of the translation inhibitor cycloheximide (fig. S5), which indicates that accumulation of the *Bs3* and *Bs3-E* transcripts was independent of de novo protein synthesis. *Agrobacterium*-mediated transient coexpression of *avrBs3* and a *Bs3-GFP* (green fluorescent protein) fusion construct under the control of the *Bs3* promoter caused GFP emission, whereas delivery of *Bs3-GFP* on its own did not result in GFP emission (fig. S6). Together these data indicate that AvrBs3 and AvrBs3Δrep16 induce transcription of the respective *R* genes *Bs3* and *Bs3-E*, and that the subsequent accumulation of these R proteins triggers HR. In agreement with this result, constitutive expression of *Bs3* or *Bs3-E* under the cauliflower mosaic virus 35S promoter triggered an *avr*-independent HR (fig. S7). We identified *Bs3* mutants with single amino acid replacements that were not compromised in protein stability but no longer triggered HR when expressed in *N. benthamiana* (fig. S8), indicating that the enzymatic activity of Bs3 is crucial to its function as a cell death inducer.

Electrophoretic mobility shift assays (EMSAs) with GST-AvrBs3 fusion protein and biotin-labeled *Bs3* and *Bs3-E* promoter fragments (Fig. 4A) showed that AvrBs3 bound to both *Bs3*- and *Bs3-E*–derived promoter fragments containing the polymorphism, although affinity appeared higher for the *Bs3*-derived fragment (Fig. 4B). Competition assays with labeled *Bs3*-derived promoter fragments and nonlabeled *Bs3*- and *Bs3-E*–derived promoter fragments, and vice versa, confirmed that AvrBs3 binds with high affinity to the *Bs3* promoter fragment and with low affinity to the *Bs3-E* promoter fragment (Fig. 4C). In contrast, AvrBs3 did not bind to a DNA fragment from a nonpolymorphic region of the *Bs3* promoter (Fig. 4B). Furthermore, EMSA studies showed that both AvrBs3 and AvrBs3Δrep16 have a higher affinity for the *Bs3* promoter than for the *Bs3-E* promoter (Fig. 4 and fig. S9). Therefore, promoter binding per se of AvrBs3 or AvrBs3Δrep16 is not the basis for promoter activation specificity.

We performed chromatin immunoprecipitation assays by infiltrating pepper ECW-30R (*Bs3*) and ECW (*Bs3-E*) leaves either with *avrBs3*-expressing *Xcv* wild-type strains or with an iso-

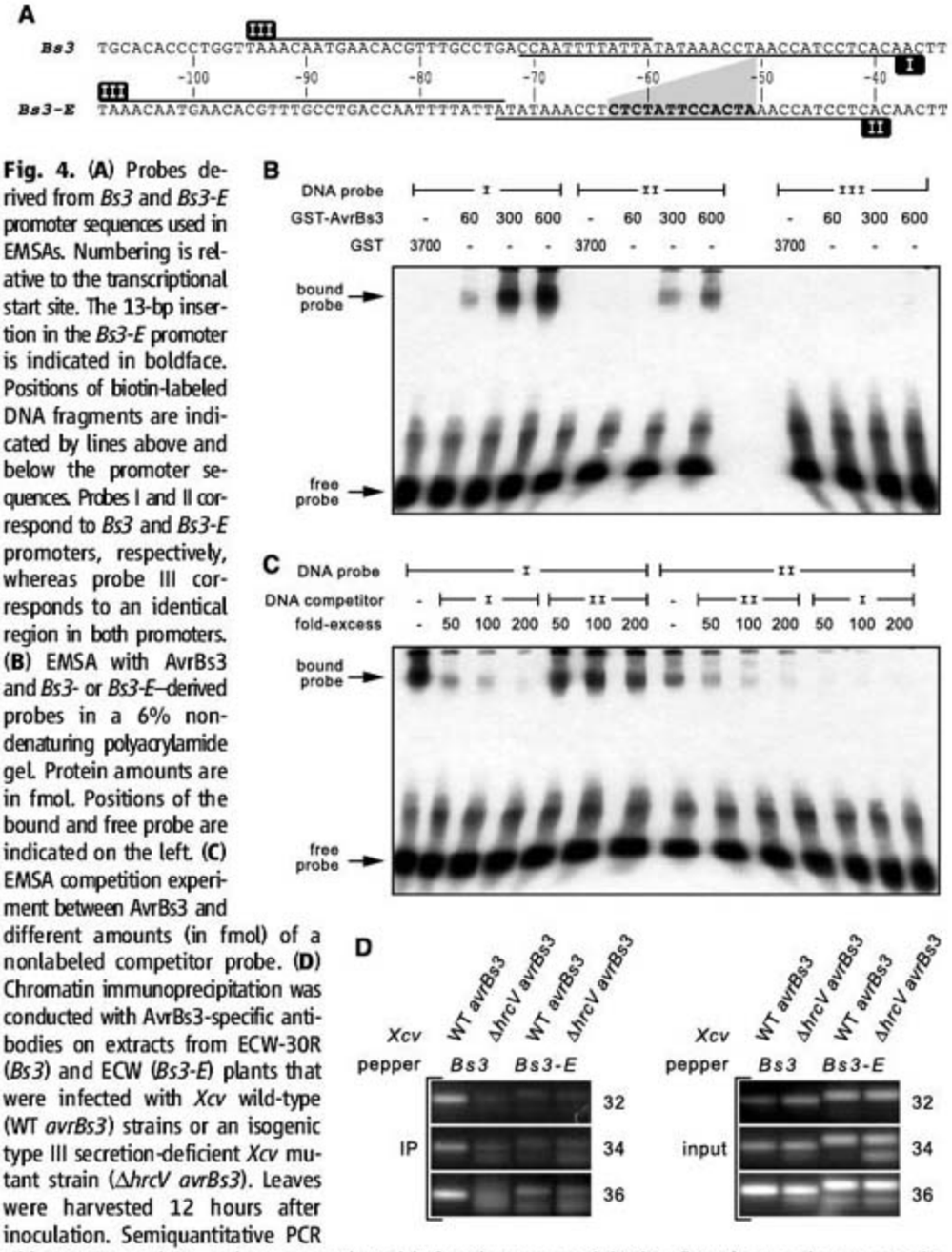

Fig. 4. (A) Probes derived from *Bs3* and *Bs3-E* promoter sequences used in EMSAs. Numbering is relative to the transcriptional start site. The 13-bp insertion in the *Bs3-E* promoter is indicated in boldface. Positions of biotin-labeled DNA fragments are indicated by lines above and below the promoter sequences. Probes I and II correspond to *Bs3* and *Bs3-E* promoters, respectively, whereas probe III corresponds to an identical region in both promoters. **(B)** EMSA with AvrBs3 and *Bs3*- or *Bs3-E*–derived probes in a 6% nondenaturing polyacrylamide gel. Protein amounts are in fmol. Positions of the bound and free probe are indicated on the left. **(C)** EMSA competition experiment between AvrBs3 and different amounts (in fmol) of a nonlabeled competitor probe. **(D)** Chromatin immunoprecipitation was conducted with AvrBs3-specific antibodies on extracts from ECW-30R (*Bs3*) and ECW (*Bs3-E*) plants that were infected with *Xcv* wild-type (WT *avrBs3*) strains or an isogenic type III secretion-deficient *Xcv* mutant strain (Δ*hrcV avrBs3*). Leaves were harvested 12 hours after inoculation. Semiquantitative PCR with 32, 34, and 36 cycles was conducted before immunoprecipitation (input) or on immunoprecipitated material (IP). ECW-30R (*Bs3*) and ECW (*Bs3-E*) derived PCR products differ in size because of a 13-bp insertion in the *Bs3-E* promoter.

genic *hrcV* mutant strain. HrcV is a conserved protein of the core T3S system with mutants incapable of delivering T3S effector proteins (*12*). After immunoprecipitation with an antibody to AvrBs3 (*13*), enrichment of the *Bs3* but not the *Bs3-E* promoter region was detected by semi-quantitative PCR (Fig. 4D). This demonstrates that *Xcv*-delivered AvrBs3 binds to the *Bs3* promoter in vivo with higher affinity than to the *Bs3-E* promoter. Given that *Bs3* promoter enrichment was detected in leaf material inoculated with the wild type but not with the *hrcV* mutant strain, we conclude that the *Bs3* promoter is bound before cell lysis.

We also infected the pepper cultivar ECW-123R containing the *R* genes *Bs1*, *Bs2*, and *Bs3* with xanthomonads delivering either the structurally unrelated AvrBs1, AvrBs2, or AvrBs3 protein or none of these Avr proteins. RT-PCR showed that the *Bs3*-derived transcripts were detectable only upon infection with *avrBs3*-expressing *Xcv* strains (fig. S10). Therefore, *Bs3* is not transcriptionally activated in the course of the *Bs1*- or *Bs2*-mediated HR.

Isolation of the pepper *Bs3* gene uncovered a mechanistically novel type of recognition mechanism and a structurally novel type of R protein that shares homology to FMOs. Recently, FMO1, an *Arabidopsis* protein that is sequence-related to Bs3 (fig. S2), was shown to be involved in pathogen defense (*14*–*16*). Thus, FMO1 and Bs3 may have similar functions. However, *FMO1* is transcriptionally induced by a variety of stimuli including virulent and avirulent microbial pathogens (*14*, *16*, *17*). In contrast, *Bs3* was not induced by virulent *Xcv* strains (Fig. 3), nor by resistance reactions mediated by the pepper *R* genes *Bs1* and *Bs2* (fig. S10). Moreover, 35S-driven *Bs3* alleles triggered an HR reaction (fig. S7), whereas a 35S-driven *FMO1* gene mediates broad-spectrum resistance but not HR (*14*, *15*). Thus, *Arabidopsis FMO1* and pepper *Bs3* differ with respect to their transcriptional regulation and function.

Our results show that the bacterial effector protein AvrBs3 binds to and activates the promoter of the matching pepper *R* gene *Bs3*. Analysis of host genes that are up-regulated by AvrBs3 ("*upa*" genes) in a compatible *Xcv*-pepper interaction (*7*, *18*) led to the identification of the *upa*-box (TATATAAACCN$_{2-3}$CC), a conserved DNA element that was shown to be bound by AvrBs3 and that is also present in the *Bs3* promoter (Fig. 1D) (*18*). This suggests that binding of AvrBs3 to the *upa*-box is crucial for activation of corresponding promoters. However, binding of an AvrBs3-like protein does not necessarily result in promoter activation, because AvrBs3Δrep16 bound with higher affinity to the *Bs3* than to the *Bs3-E* promoter (fig. S9) but only activated the *Bs3-E* and not the *Bs3* promoter (Fig. 3). Because AvrBs3Δrep16 and AvrBs3 differ in their structure, we postulate that upon DNA binding, their functional domains (e.g., AD) are exposed at different promoter locations, which may define whether AvrBs3Δrep16 and AvrBs3 are able to activate a given promoter. Additionally, given that the *Bs3* promoter determines recognition specificity, the *Bs3* promoter might be coevolving to maintain compatibility with rapidly changing AvrBs3-like proteins, similar to that seen in the NB-LRR proteins (*19*, *20*).

We consider it likely that not only AvrBs3 but also other AvrBs3 homologs bind to and activate promoters of matching *R* genes. The recently isolated rice *R* gene *Xa27*, which mediates recognition of the AvrBs3-like AvrXa27 protein from *Xanthomonas oryzae* pv. *oryzae* (*21*), is transcriptionally induced by AvrXa27, and thus it is tempting to speculate that the *Xa27* promoter is a direct target of AvrXa27. However, whether AvrXa27 acts directly at the *Xa27* promoter remains to be clarified.

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A Bacterial Effector Acts as a Plant Transcription Factor and Induces a Cell Size Regulator

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Pathogenicity of many Gram-negative bacteria relies on the injection of effector proteins by type III secretion into eukaryotic cells, where they modulate host signaling pathways to the pathogen's benefit. One such effector protein injected by *Xanthomonas* into plants is AvrBs3, which localizes to the plant cell nucleus and causes hypertrophy of plant mesophyll cells. We show that AvrBs3 induces the expression of a master regulator of cell size, *upa20*, which encodes a transcription factor containing a basic helix-loop-helix domain. AvrBs3 binds to a conserved element in the *upa20* promoter via its central repeat region and induces gene expression through its activation domain. Thus, AvrBs3 and likely other members of this family provoke developmental reprogramming of host cells by mimicking eukaryotic transcription factors.

Gram-negative phytopathogenic bacteria of the genus *Xanthomonas* cause a broad variety of diseases in crop plants (*1*). Pathogenicity depends on the translocation of effector proteins directly into the plant cell cytosol by a type III secretion (T3S) system (*2*). The AvrBs3 family is a prominent effector class in *Xanthomonas* spp. (*3*), comprising major virulence determinants (*4*–*6*). These effectors are characterized by a central repeat region, nuclear localization signals (NLSs), and an acidic transcriptional activation domain (AD) (*3*). AvrBs3 was isolated from *X. campestris* pv. *vesicatoria* (*Xcv*), the causal agent of bacterial spot disease on pepper and tomato (*7*). In susceptible host plants and other solanaceous species, AvrBs3 elicits hypertrophy (i.e., enlargement) of mesophyll cells (*8*) and also contributes to the dispersal of *Xcv* between pepper plants under field conditions (*9*). Cell enlargement is also found in other complex disease phenotypes [e.g., citrus canker elicited by the AvrBs3-like effector PthA from *X. axonopodis* pv. *citri* (*10*) and *Pantoea agglomerans*–induced gall formation (*11*)].

AvrBs3 has a central region consisting of 17.5 nearly identical 34–amino acid repeats [which determine the specificity of protein activity in plants (*8*, *12*)], functional NLSs, and an AD in its C terminus (*13*–*15*)—all of which are essential for AvrBs3 activity. Furthermore, AvrBs3 forms homodimers (*16*) and appears to be a transcription factor localized to the plant cell nucleus (*8*, *13*–*15*). Pepper *upa* (upregulated by AvrBs3) genes that are induced by AvrBs3 encode, amongst others, putative α-expansins and auxin-induced proteins that might be involved in the induction of hypertrophy (*8*). However, most *upa* genes are indirect targets of AvrBs3 because their induction requires de novo synthesis of plant proteins (*8*).

To isolate *upa* genes that are direct targets of AvrBs3, we infected susceptible pepper plants [cultivar Early Calwonder (ECW)] with *Xcv* strain 85-10 expressing *avrBs3* or carrying an empty vector in the presence of cycloheximide, which blocks eukaryotic protein synthesis. cDNA fragments corresponding to AvrBs3-induced pepper genes were identified by suppression-subtractive hybridization and confirmed by reverse Northern analysis and reverse transcription polymerase chain reaction (RT-PCR). Among these cDNAs, we detected the previously identified *upa10* and *upa11* genes (*8*), validating our approach, as well as previously unrecognized AvrBs3-induced genes. One gene, designated *upa20*, encodes a putative transcription factor of the basic helix-loop-helix (bHLH) family and was chosen for further analysis.

We isolated the full-length cDNA of *upa20* by rapid amplification of cDNA ends (RACE)–PCR and determined the corresponding genomic sequence from a pepper BAC (bacterial artificial chromosome) library (*17*). *upa20* has a complex gene structure comprising eight exons and seven introns (Fig. 1A) and encodes a putative 340–amino acid bHLH transcription factor with a predicted molecular mass of 37.8 kD. The bHLH domain, which generally serves as DNA binding and dimerization domain (*18*), is located in the region from amino acids 167 to 225 (Fig. 1B). BLASTP analyses show that Upa20 is most related to an uncharacterized protein from rice (Os09g0510500; accession BAF25548.1; 48% identity and 63% similarity over 240 amino acids) and is also similar to BIGPETALp (BPEp) from *Arabidopsis* (accession CAK32499.1; 55% identity and 70% similarity over 134 amino acids), which is involved in the control of petal size (*19*).

To address the role of *upa20* in the induction of hypertrophy, we performed virus-induced gene silencing of *upa20* in *Nicotiana benthamiana*, which severely reduced the normally strong AvrBs3-dependent hypertrophy, the result of which was visible as pustules on the lower leaf surface (Fig. 2, A and B). *Agrobacterium*-mediated *upa20* expression demonstrated that Upa20 alone induces hypertrophy in *N. benthamiana* and other solanaceous plants (Fig. 2C and fig. S1). In *upa20*-expressing tissue of *N. benthamiana*, palisade and spongy parenchyma cells were strongly enlarged as compared with those in tissue of the control (Fig. 2, D and F). The hypertrophy reaction was phenotypically similar to tissue transiently expressing *avrBs3* (Fig. 2E) but was faster and stronger. Further observations revealed cell wall invaginations exclusively in *upa20*-expressing tissue, suggesting that cell wall synthesis is increased (Fig. 2, G and H). In addition, chloroplasts of *upa20*-expressing cells showed a decrease in starch content (Fig. 2, I and J) in accordance with cell enlargement being a highly energy-consuming process. Therefore, our re-

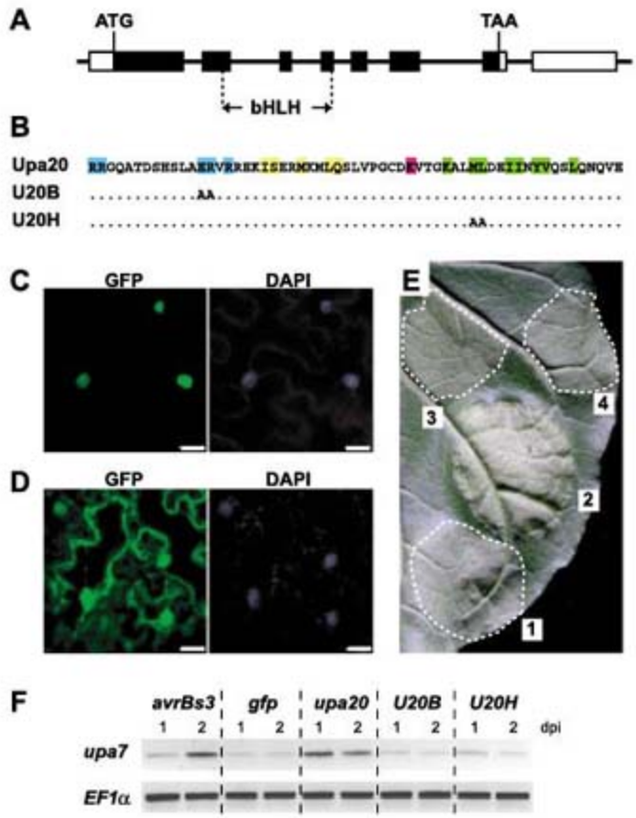

Fig. 1. (**A**) Structure of *upa20* in pepper. Coding and noncoding exons are indicated as black and white rectangles, and introns are indicated as black lines between the exons. (**B**) Amino acid sequence (*30*) of the Upa20 bHLH region (amino acids 167 to 225). The amino acids that define the bHLH motif (*18*) are color-coded (basic region, blue; first helix, yellow; loop, pink; and second helix, green). Conserved amino acids were changed to alanine in the basic region (U20B) and in the HLH dimerization motif (U20H). (**C** and **D**) Confocal laser scanning microscopy of *N. benthamiana* 2 days after *Agrobacterium*-mediated transfer of *upa20::gfp* (C) or *gfp* (D). 4′,6′-Diamidino-2-phenylindole (DAPI) staining indicates nuclei. Scale bars, 20 μm. (**E**) *N. benthamiana* transiently expressing *gfp* (1), *upa20::c-myc* (2), *U20B::c-myc* (3), and *U20H::c-myc* (4), 8 days post-infiltration (dpi). (**F**) Upa20 induces the expression of *upa7*, encoding a putative α-expansin. RT-PCR analysis of susceptible pepper plants 1 and 2 dpi of *Agrobacterium* delivering *avrBs3*, *gfp*, *upa20*, *U20B*, and *U20H*, respectively, is shown. *EF1α* was used as control for equal cDNA amounts.

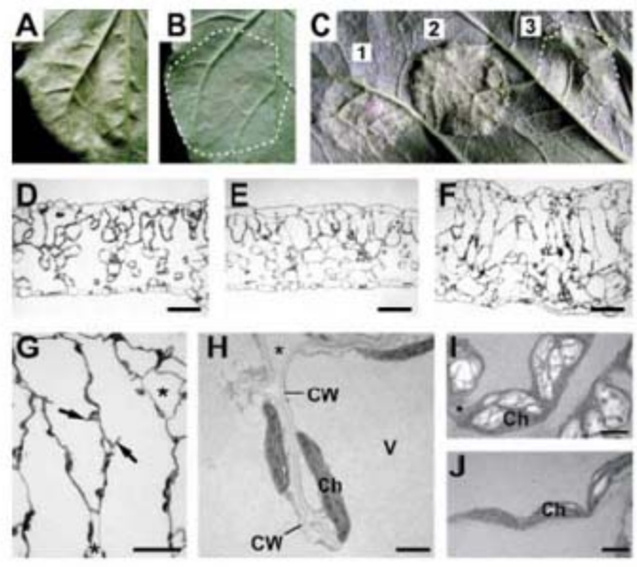

Fig. 2. (**A** and **B**) Transient expression of *avrBs3* elicits a hypertrophy in *gfp*-silenced (A), but not in *upa20*-silenced (B), *N. benthamiana* leaves, 11 dpi. (**C**) *Agrobacterium*-mediated expression of *avrBs3* (1) and *upa20* (2) causes hypertrophy in *N. benthamiana* 7 dpi relative to control [empty transferred DNA (T-DNA) (3)]. (**D** to **F**) Light microscopy of *N. benthamiana* leaves 4 days after *Agrobacterium*-mediated delivery of empty T-DNA (D), *avrBs3* (E), and *upa20* (F). (**G**) Higher magnification of a sector in (F). Arrows indicate cell wall invaginations. (**H**) Electron micrograph of a cell wall invagination of an *N. benthamiana* palisade cell expressing *upa20*, 4 dpi. Asterisks in (G) and (H) mark apoplastic spaces. (**I** and **J**) Chloroplasts of *N. benthamiana* cells 3 dpi with *Agrobacterium* delivering an empty T-DNA (I) or *upa20* (J). Scale bars correspond to 100 μm [(D) to (F)], 30 μm (G), and 2 μm [(H) to (J)], respectively. Ch, chloroplast; CW, cell wall; V, vacuole.

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sults suggest that Upa20 is a master regulator of cell enlargement that stimulates cell growth, in contrast to BPEp from *Arabidopsis*, which reduces cell size (*19*). Consistent with its predicted function as a transcription factor, N- and C-terminal green fluorescent protein (GFP) fusions of Upa20 were exclusively localized to the nucleus, where they often concentrated in distinct foci (Fig. 1C and fig. S2). These foci are reminiscent of nuclear speckles, which may be storage and assembly areas of transcription and splicing factors, supplying them to active transcription sites (*20*). When the basic region (U20B) and the dimerization domain (U20H) of Upa20 were altered (Fig. 1B), both mutants failed to cause hypertrophy in *N. benthamiana* (Fig. 1E), although all proteins were expressed in similar amounts (fig. S3).

Together, these results suggest that Upa20 is a bona fide bHLH transcription factor. We wondered whether any of the previously identified *upa* genes are target genes of Upa20. Induction of *upa1* to *upa9*, expression of which requires de novo protein synthesis, starts 6 to 9 hours after infection of pepper plants with *Xcv* delivering AvrBs3 (*8*), whereas *upa20* induction starts within 3 to 4 hours post-infection (hpi) (fig. S4). RT-PCR was performed with RNA from susceptible pepper plants transiently expressing *upa20* and the *upa20* bHLH mutants along with controls. Upa20 activated the expression of *upa7*, encoding a putative α-expansin, which was shown to be dependent on the bHLH domain of Upa20 (Fig. 1F). However, the other genes tested were not consistently induced by Upa20, suggesting that AvrBs3 activates additional genetic pathways.

Our results indicate that the visible consequence of AvrBs3 virulence activity in susceptible plants, the induction of cell hypertrophy, is caused by AvrBs3 targeting *upa20*, a regulator of cell enlargement. To elucidate the mechanism of *upa20* induction, we tested for the requirement of the eukaryotic motifs in AvrBs3. Pepper plants infected with *Xcv* expressing *avrBs3* and mutant derivatives clearly showed that both the NLSs and AD are required for gene activation (fig. S5). In addition, deletion of four repeats abolished *upa20* induction (fig. S5), demonstrating that the central repeat region of AvrBs3 is indispensable for function. Similarly, the AvrBs3 homolog AvrBs4, which differs from AvrBs3

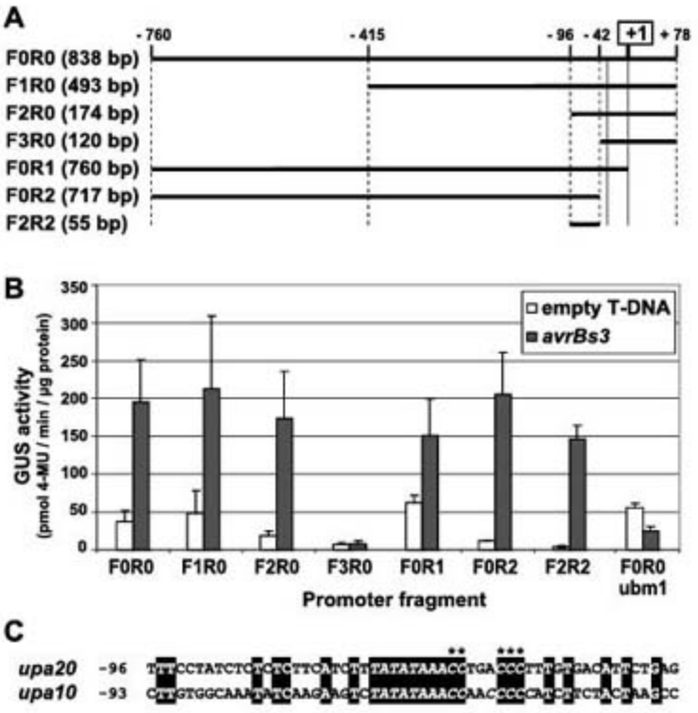


Fig. 3. (**A**) Promoter fragments tested for AvrBs3 inducibility. The transcriptional start sites, in the presence of AvrBs3 (+1) and predominantly used in the absence of AvrBs3 (37 bp upstream of +1), are indicated with solid vertical lines. The transcription start of F0R2 was mapped to the *att*B2 site of the construct. Dashed lines and numbers above indicate positions with respect to +1. (**B**) GUS assays show AvrBs3 inducibility of the *upa20* promoter in *N. benthamiana*. Promoter fragments shown in (A) and a *upa* box mutant derivative of F0R0, F0R0ubm1 [see (C)], were cloned in front of a *egfp::uidA* reporter and tested by codelivery with *avrBs3* and empty T-DNA. 4-MU, 4-methylumbelliferone. Error bars indicate SD. (**C**) The smallest AvrBs3-responsive *upa20* promoter fragment (F2R2) (top row) as compared with a corresponding region in the *upa10* promoter. Numbers refer to the transcriptional start site (+1) in the presence of AvrBs3. Nucleotides that belong to the proposed *upa* box are indicated in italics. Asterisks mark nucleotides that were changed to G in mutant ubm1.

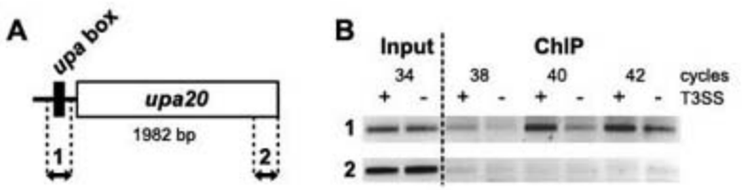
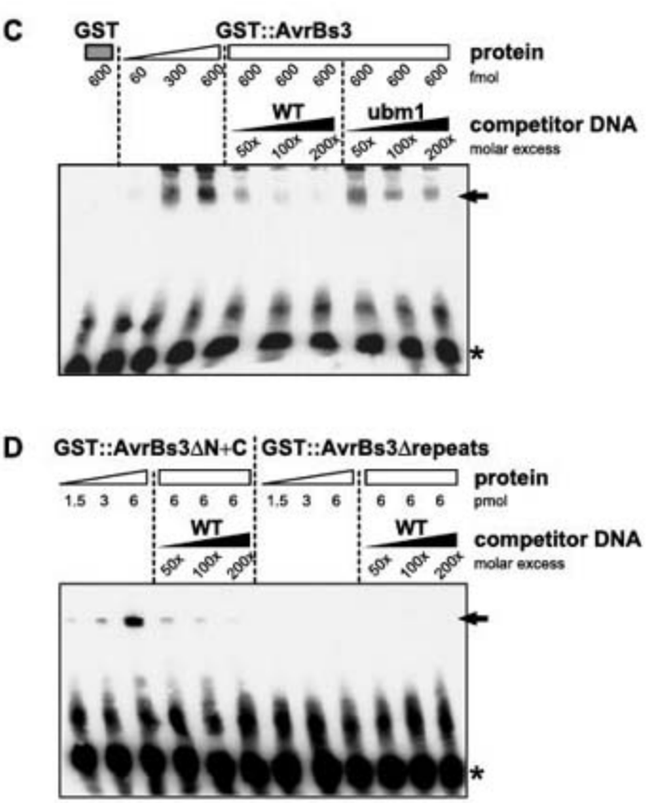


Fig. 4. (**A**) Fragments in the pepper *upa20* region analyzed by ChIP. (**B**) ChIP analysis of pepper ECW 12 hpi with *Xcv* strain 82-2 (+T3SS) and the T3S system mutant 82-8Δ*hrcV* (–T3SS). Fragments surrounding [(1); 197 bp] and downstream of the *upa* box [(2); 209 bp] [see (A)] were amplified with cycle numbers as indicated. (**C**) EMSA with increasing molar amounts of GST::AvrBs3 incubated with 50 fmol biotin-labeled 36-bp *upa20* promoter fragments containing the *upa* box. The control is GST. Unlabeled WT fragments and fragments with a mutated *upa* box (ubm1, see Fig. 3C) were used as competitor DNA. (**D**) EMSA of 50 fmol biotin-labeled WT promoter fragment incubated with increasing amounts of GST::AvrBs3ΔN+C (AvrBs3 repeat region) and GST::AvrBs3Δrepeats. Unlabeled WT DNA fragments were used for competition. Arrows, bound probe; asterisks, free probe. The uppermost signals correspond to DNA in the slots. For expression of the GST fusion proteins, see fig. S9.



mainly in the repeat region (*21*), does not enhance *upa20* expression, which is in agreement with the finding that AvrBs3 deletion derivatives and AvrBs4 do not induce a hypertrophy (*8*).

To identify an AvrBs3-responsive DNA element, we isolated the promoter and determined the transcription start site of *upa20*. Comparison of cDNA sequences revealed that, in the presence of AvrBs3, transcription of *upa20* starts 37 base pairs (bp) downstream of the prevalent start site used for the basal level of *upa20* transcription under non-inducing conditions (fig. S6). Upstream of both transcription start sites, a TATA box motif is located (fig. S6). These data suggest that *upa20* undergoes alternative transcriptional initiation, which has been reported for a wide range of eukaryotic genes (*22*, *23*) and is probably mediated by the action of different transcription factors.

To analyze the AvrBs3 inducibility of the *upa20* promoter, we used a promoterless *egfp::uidA* cassette as a reporter in *N. benthamiana* after *Agrobacterium*-mediated transformation. β-Glucuronidase (GUS) activities and GFP fluorescence revealed that the *upa20* promoter is AvrBs3-responsive (Fig. 3B and fig. S7). Promoter deletions from both ends limited the AvrBs3-responsive region to a 55-bp sequence (Fig. 3, A and B). We searched for sequence similarities in the promoters of other putative direct targets of AvrBs3, concentrating on *upa10* (*8*). The *upa10* promoter was isolated from pepper ECW by genome walking and revealed a motif in common with the *upa20* promoter that we termed the *upa* box (Fig. 3C). This motif contains a TATA box followed by two stretches of cytosine residues, separated by two and three other nucleotides, respectively. We exchanged all cytosines (Cs) of the motif with guanines (Gs) (asterisks in Fig. 3C; this mutant was designated ubm1), which abolished the induction of the reporter gene by AvrBs3 without affecting the basal activity of the *upa20* promoter. Notably, the *upa* box is also present in the promoter of the *Bs3* resistance gene, whose activation by AvrBs3 leads to the induction of cell death in the resistant pepper line ECW-30R (*24*). In susceptible ECW plants, a 13-bp insertion between the two C stretches in the *upa* box also abolishes gene induction (*24*).

We performed chromatin immunoprecipitation (ChIP) with an AvrBs3-specific antibody (*25*) to determine whether AvrBs3 associates with the *upa20* promoter in planta. Chromatin was isolated from pepper ECW infiltrated with *Xcv* strain 82-8 naturally expressing *avrBs3* and a T3S mutant derivative (82-8Δ*hrcV*) that expresses *avrBs3* but is not able to translocate effector proteins into the plant cell (*26*). AvrBs3 precipitated with the *upa20* promoter containing the *upa* box but not with a sequence located 2 kb downstream of the *upa* box (Fig. 4, A and B). This demonstrates that DNA binding is specific, albeit it is not clear whether AvrBs3 binding is mediated by a plant protein.

Although AvrBs3 does not contain a classical DNA binding domain (*3*), we tested whether it directly interacts with the *upa20* promoter DNA in electrophoretic mobility shift assays (EMSAs) with a 36-bp biotin-labeled *upa20* promoter fragment containing the *upa* box. Addition of GST::AvrBs3 identified a protein-DNA complex with levels that increased as increasing amounts of fusion protein were added, whereas glutathione *S*-transferase (GST) alone failed to bind DNA (Fig. 4C). The band shift was competed when unlabeled *upa* box DNA was added, whereas the ubm1 fragment (Fig. 3C) competed in binding to a much lesser extent (Fig. 4C), demonstrating that AvrBs3 is specifically binding to the *upa* box. In addition, EMSA with a biotin-labeled ubm1 fragment confirmed a weaker binding of AvrBs3 to the mutant as compared with that to the wild-type (WT) sequence (fig. S8A), and this binding was competed more efficiently by the unlabeled WT sequence than by the unlabeled ubm1 fragment (fig. S8B).

An AvrBs3 derivative consisting of only the repeat region bound the *upa20* promoter fragment in EMSA, albeit less efficiently than the WT protein. In contrast, a protein containing the N and C termini of AvrBs3 but lacking the repeats did not bind (Fig. 4D). These data suggest that the 17.5 repeats in the central region of AvrBs3 mediate the specific interaction with DNA, which is consistent with the fact that the repeat region determines the specificity of AvrBs3 activity (*8*, *12*), including *upa20* induction (fig. S5). The AvrBs3 family member AvrXa7 shows an in vitro DNA binding activity with a preference for adenine-thymine (AT)–rich DNA (*27*). Our finding (that C-to-G mutations without change in AT content affected both binding of AvrBs3 in vitro and activation of the *upa20* promoter in planta) demonstrates that specificity, not base composition, determines binding.

Previously, induction of host genes has been reported for the AvrBs3-like effectors PthXo1 and AvrXa27 from the rice pathogen *X. oryzae* pv. *oryzae*. Both proteins differentially induce rice genes on the basis of their promoter variations (*28*, *29*). Sequence polymorphisms are located within 80 bp upstream of the transcription start sites (*28*, *29*) (i.e., in a similar position relative to the *upa* box in AvrBs3-responsive promoters). However, the *upa* box is not found in the rice gene promoters, suggesting that AvrBs3-like proteins have different DNA binding specificities, which are mediated by the corresponding repeat regions. The nearly identical repeats of AvrBs3-like effectors usually differ at amino acid positions 12 and 13 (*3*); hence, these amino acids might be involved in the specific interaction with DNA. How the highly similar effector proteins confer different DNA binding specificities is enigmatic and awaits the structural analysis of AvrBs3 and its homologs. In light of our data, we propose that the molecular principle of AvrBs3 action may be common to other members of this large and important family of type III effectors in bacterial plant pathogens.

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30. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

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Supporting Online Material

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A Linear Pentapeptide Is a Quorum-Sensing Factor Required for *mazEF*-Mediated Cell Death in *Escherichia coli*

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mazEF is a toxin-antitoxin module located on many bacterial chromosomes, including those of pathogens. Here, we report that *Escherichia coli mazEF*-mediated cell death is a population phenomenon requiring a quorum-sensing molecule that we call the extracellular death factor (EDF). Structural analysis revealed that EDF is a linear pentapeptide, Asn-Asn-Trp-Asn-Asn. Each of the five amino acids of EDF is important for its activity.

Programmed cell death (PCD) is generally associated with eukaryotic multicellular organisms (*1*, *2*). However PCD systems have also been observed in bacteria (*3*–*11*). One of these systems is mediated by the toxin-antitoxin module (*mazEF*) located in many bacterial chromosomes (*11*–*13*) and mainly studied in *Escherichia coli* (*3*, *10*, *11*). *E. coli mazF* encodes a stable toxin, MazF (*3*), which is a sequence-specific endoribonuclease that preferentially cleaves single-stranded mRNAs at ACA sequences (*14*). *mazE* encodes a labile antitoxin, MazE, that counteracts the action of MazF (*3*). *E. coli mazEF* is a stress-induced toxin-antitoxin module. Thus, any stressful condition that prevents the expression of *mazEF* will lead to a reduction of MazE levels in the cell, permitting the MazF toxin to act. Such stresses include the transient inhibition of transcription and/or translation by antibiotics such as rifampicin, chloramphenicol, and spectinomycin, as well as DNA damage caused by thymine starvation, mitomycin C, nalidixic acid, and ultraviolet irradiation (*15*, *16*).

We previously suggested that *E. coli mazEF*-mediated cell death is a population phenomenon (*11*). Here we confirm that *E. coli mazEF*-mediated cell death was dependent on the density of the bacterial population (fig. S1). Adding rifampicin for a short period to inhibit transcription led to *mazEF*-mediated cell death at densities of 3×10^8 or 3×10^7 cells/ml, but not at 3×10^5 or 3×10^4 cells/ml (fig. S1). Consequently, we examined whether the supernatant of a dense culture could restore *mazEF*-mediated cell death in a diluted culture. To this end, we added the supernatant of a dense culture to a diluted culture and then induced *mazEF*-mediated cell death by addition of rifampicin (Fig. 1A), chloramphenicol (fig. S2A), or trimethoprim (fig. S2B). We concluded that *mazEF*-mediated cell death requires an "extracellular death factor" (EDF). We observed EDF activity in *E. coli* cultures during logarithmic growth but not during stationary growth (fig. S3). This finding correlates with our previous results showing that *E. coli mazEF*-mediated cell death occurs during exponential phase but not during stationary phase (*15*). Here, we show that stationary-phase resistance to PCD results from a lack of EDF activity.

Our preliminary characterization of EDF revealed that it is sensitive to extreme pH (Fig. 1B), high temperatures (80° to 100°C) (fig. S4A), and proteinase K (fig. S4B). For chemical characterization we purified EDF from a large volume of a supernatant of an *E. coli* mid-exponential phase culture grown in a minimal medium. The supernatant was collected and fractions were separated on a C-18 SepPak cartridge (fig. S5) (*17*). Active fractions were purified by high-performance liquid chromatography (HPLC), and EDF activity comigrated with a single peak with an elution time of 20 min (Fig. 1, C and D). To avoid damaging EDF in acidic conditions (Fig. 1B), we performed electrospray ionization mass spectrometry (ESI-MS) at neutral pH and obtained a peak of 661 daltons (Fig. 2A). This peak was not observed during standard MS analysis at pH 2.5 (fig. S6). Fragmentation (MS/MS) analysis of the material from this 661-dalton peak revealed that EDF is a linear peptide with the amino acid sequence Asn-Asn-Trp-Asn-Asn (NNWNN) (Fig. 2, B and D). The four Asn residues in EDF are vulnerable to deamidation under acidic conditions (*18*) normally used for ESI-MS.

To test whether the NNWNN peptide is indeed EDF, we chemically synthesized an iden-

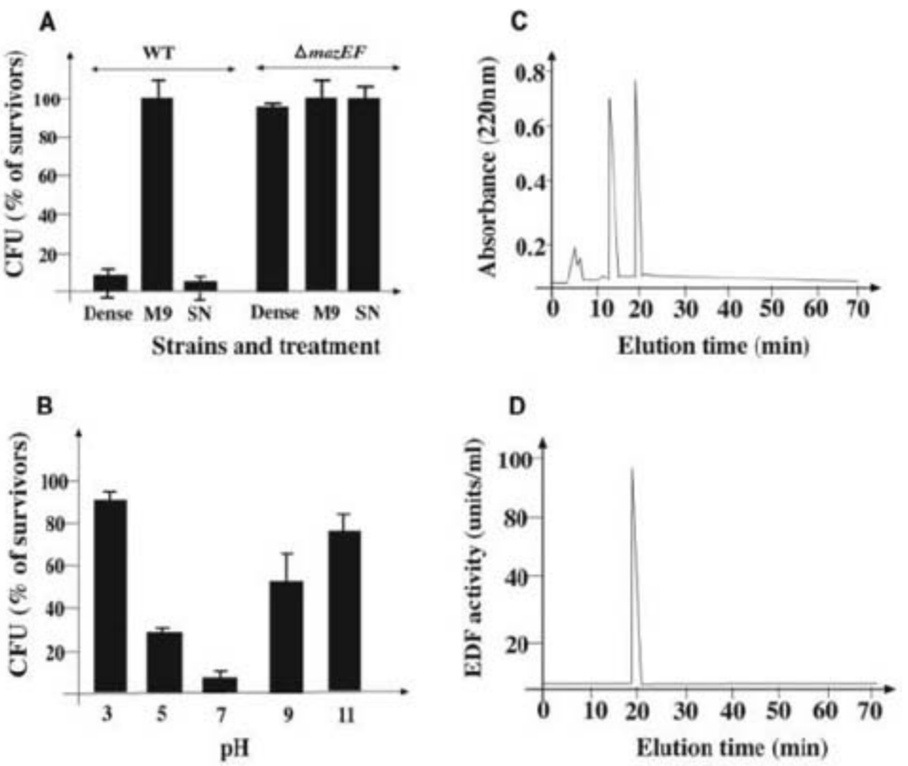

Fig. 1. (**A**) A supernatant of a dense culture can restore *mazEF*-mediated cell death to a diluted culture. *E. coli* MC4100*relA*$^+$ (wild type, WT) and MC4100*relA*$^+$Δ*mazEF* (Δ*mazEF*) were grown logarithmically (*17*). At a density of 2.5×10^8 cells/ml, samples were either not diluted (dense) or diluted to a density of 3×10^4 cells/ml in prewarmed M9 medium (M9) or in a prewarmed supernatant of a dense culture (SN) (*17*). The samples were incubated without shaking at 37°C for 10 min and for another 10 min with rifampicin (10 μg/ml). CFU, colony-forming units. (**B**) Effects of various pHs on the SN. SN was incubated at pH 3, 5, 7, 9, or 11 for 2 hours and titrated to pH 7. Its ability to restore *mazEF*-mediated cell death to a diluted culture was determined as in (A). (**C**) Milliabsorbance at 220 nm, determined during elution from the HPLC column of the purified supernatant (fig. S5). (**D**) EDF activity plotted as a function of elution time from the HPLC column.

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tical peptide and tested it for biological activity. When added to a diluted *E. coli* culture, the synthetic peptide enabled *mazEF*-mediated cell death when induced in different *E. coli* strains by rifampicin (Fig. 2C and fig. S7) and by several other stressful conditions (fig. S8). At a wide range of concentrations (2.5 to 200 ng/ml), the killing activity of the chemically synthesized EDF was *mazEF*-dependent; virtually no EDF activity was observed in a *mazEF* knockout strain (Fig. 3). We further confirmed the *mazEF* dependence of EDF by transforming the *mazEF* knockout strain with a plasmid harboring the *mazEF* module. The presence of this module on the plasmid completely restored the killing activity of EDF (Fig. 3). Note that at higher concentrations of EDF (>200 ng/ml), we observed a reduction of viability even in the *mazEF* knockout strain (Fig. 3). We assume that at high concentrations, EDF acts less specifically, possibly by inducing some other PCD systems or by inactivating other essential components.

To determine the role of each residue in EDF activity, we prepared five synthetic peptides, each with a Gly replacing one of the amino acids in the natural EDF sequence, and examined their biological activity in the wild-type strain. Changing the first or fifth amino acid abolished EDF killing activity, whereas changing the second, third, or fourth amino acid led to a moderate reduction in killing activity (Fig. 4A). Thus, each amino acid in EDF is important for its activity, with the N- and C-terminal residues being the most critical. A similar hierarchy of amino acid importance was obtained when we examined whether mutant EDF molecules are able to inhibit wild-type EDF activity (fig. S9). EDFs mutated at the terminal amino acids (1 and 5) were efficient inhibitors of EDF activity (fig. S9); however, mutated EDF peptides in which glycine replaced the amino acids in positions 2, 3, or 4 inhibited EDF activity only when the concentration of wild-type EDF was low. These results (Fig. 4A and fig. S9) indicated that amino acids 1 and 5 had roles similar to each other, as did amino acids 2 through 4.

We further examined several characteristics of EDF required for its activity. Using synthetic peptides (Fig. 4B), we found that (i) the tripeptide NWN does not have EDF activity, whereas the heptapeptide NNNWNNN has partial activity; (ii) the presence of the same amino acid at external positions 1 and 5 of EDF seems to be important, and EDF activity was only partially reduced with Gly instead of Asn at these positions; and (iii) the presence of an amide at the external positions probably has a role in EDF activity, as the replacement of Asn by Gln (Q) at either end of the pentapeptide (QNWNN or NNWNQ)—that is, a substitution that carries an

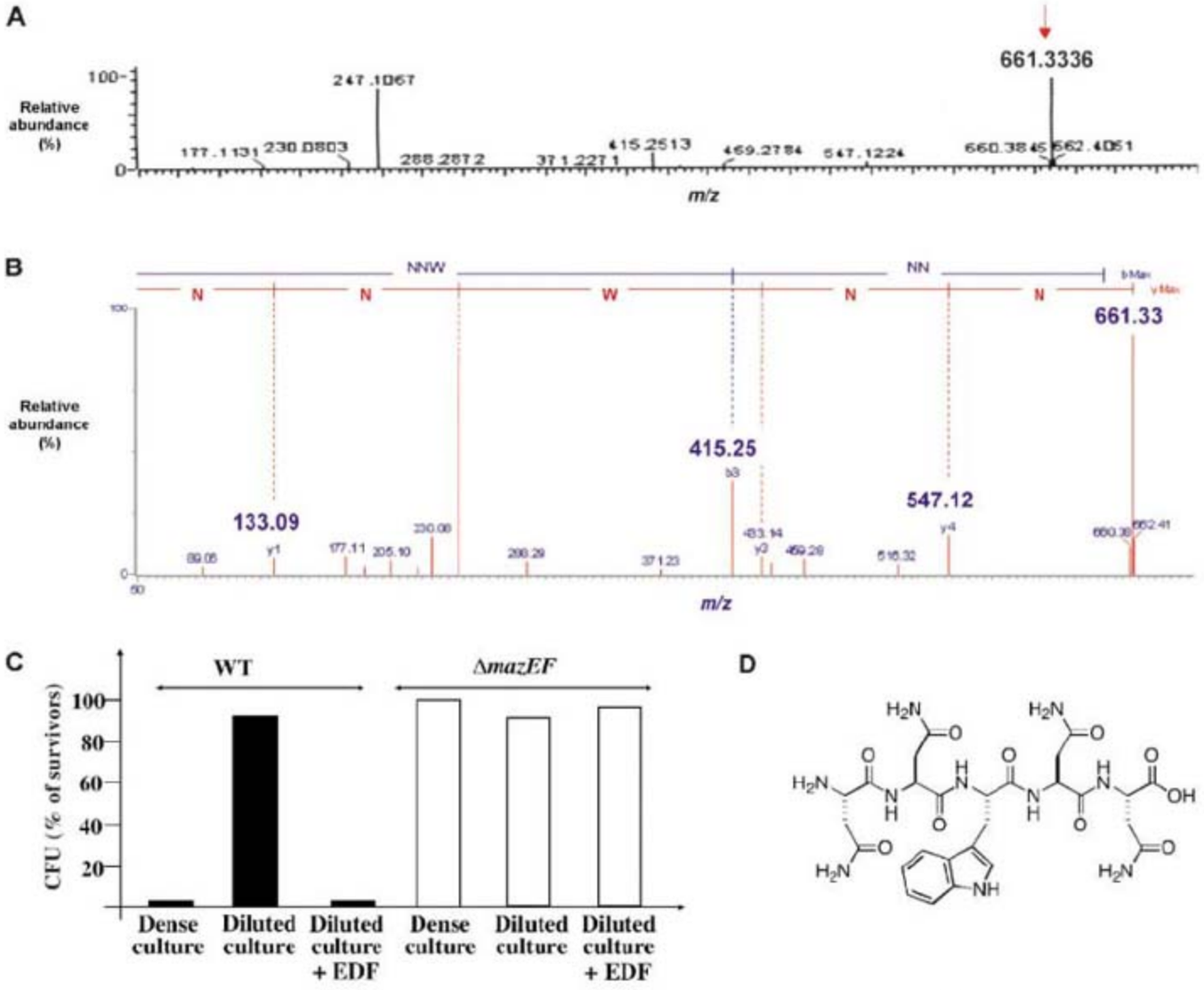

Fig. 2. The chemical nature of EDF identified by mass spectrometry. The chemical composition of the purified peak found to have EDF activity was carried out by ESI-MS (QTof2 Micromass instrument). **(A)** Peaks ranging from 200 to 662 MW, among them one of 661 MW (marked by an arrow). **(B)** The MS/MS spectrum of the 661-MW peak revealed a peptide with the amino acid sequence NNWNN. **(C)** The chemically synthesized EDF-NNWNN can restore *mazEF*-mediated cell death to a diluted culture. *E. coli* MC4100*relA*$^+$ cells were grown as in Fig. 1A. At a density of 2.5×10^8 cells/ml, samples were either not diluted (dense) or diluted to 3×10^4 cells/ml in prewarmed M9 medium (diluted culture) or in a prewarmed M9 applied with chemically synthesized EDF (2.5 ng/ml) (diluted culture + EDF). Samples were incubated with rifampicin as in Fig. 1A. **(D)** Structure of EDF as determined by nuclear magnetic resonance analysis (table S1).

amide and is structurally related to Asn—led to only a partial reduction in EDF activity. We conclude that NNWNN appears to be the optimal sequence for EDF function.

Using database analysis, we searched the *E. coli* genome for DNA sequences corresponding to the amino acid sequence NNWNN. To our surprise, only five open reading frames predicted peptide similarity to NNWNN (fig. S10). The deletion of only two genes prevented the production of an active EDF (fig. S11): *zwf* encoding NNWDN (D = Asp) and *ygeO* encoding NNWN. The *zwf* product, carrying the sequence NNWDN, may be the precursor of EDF, and a subsequent amidation step may generate the full NNWNN sequence. Amidation may occur either before or after the cleavage of the precursor by one of *E. coli* proteases. Our results indicated that Asn synthetase A (*19*) is involved; deleting the gene *asnA* prevented production of active EDF, whereas deleting *asnB* (encoding Asn synthetase B) did not (fig. S11). In addition, our results revealed that the product of *ygeO* gene is also involved in the generation of EDF (fig. S11).

Bacteria communicate with one another via a variety of quorum-sensing signal molecules, or autoinducers, which have been found to be involved in bioluminescence, virulence, biofilm formation, sporulation, mating, and competence for DNA uptake, among other responses (*20*–*25*). Quorum sensing provides a mechanism for bacteria to monitor each other's presence and to modulate gene expression in response to population density. Our results show that *mazEF*-mediated cell death is a quorum-sensing process in which the EDF peptide is the autoinducer. The cellular component(s) directly interacting with EDF are currently under investigation, as are the specific stage(s) in the *mazEF*-mediated death network that is affected. The quorum-sensing process involved in *mazEF*-mediated cell death is of interest for two reasons: (i) No other peptide besides EDF, to our knowledge, has been reported to be involved in quorum sensing in *E. coli*, and (ii) EDF appears to be a type of peptide distinct from those known to be involved in quorum sensing among Gram-positive bacteria, because EDF is synthesized from an enzyme (Zwf) (*23*, *24*) and because it is involved in bacterial PCD.

Increasing experimental evidence indicates that bacteria seldom behave as isolated organisms, and in nature they more often exist as communities capable of intercellular communication and concerted social behavior (*21*, *25*, *26*). We previously suggested that bacterial PCD is yet another manifestation of bacterial multicellularity (*11*) and have shown that *mazEF* prevents the spread of phage infection (*27*). Here we report that *E. coli mazEF*-directed bacterial death is mediated by an extracellular pentapeptide (EDF) and that bacterial PCD appears to depend on cell-to-cell communication. When challenged by stressful conditions that trigger *mazEF*-mediated cell death, the bacterial population can act like a multicellular organism in which a subpopulation of cells dies and releases nutrients (*11*) and/or signaling molecules, and/or clears phages (*27*), thereby permitting the survival of the bacterial population as a whole. In addition, the death of a subpopulation may enable biofilm formation by the release of component(s) providing the biofilm matrix (*28*). Finally, on a practical level, the ability to chemically synthesize an identical peptide carrying EDF activity may be a lead for a new class of antibiotics that specifically trigger bacterial cell death.

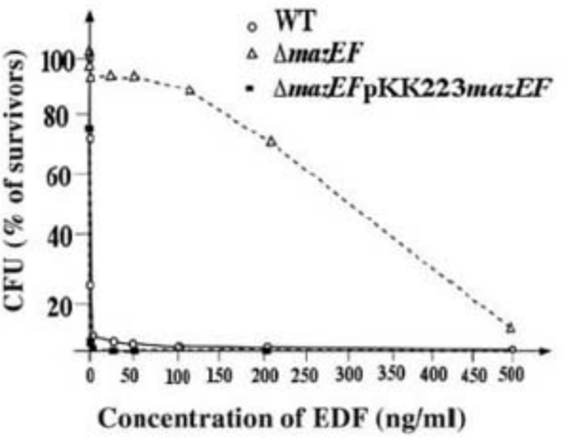

Fig. 3. The response to chemically synthesized EDF is *mazEF*-dependent. *E. coli* MC4100*relA*$^+$ (WT), MC4100*relA*$^+$ Δ*mazEF* (Δ*mazEF*), and MC4100*relA*$^+$ Δ*mazEF* pKK223*mazEF* (Δ*mazEF* pKK223*mazEF*) were grown as in Fig. 1A. Strain MC4100*relA*$^+$Δ*mazEF* pKK223*mazEF* was grown in M9 applied with ampicillin (100 μg/ml). At a density of 2.5×10^8 cells/ml, samples were diluted in prewarmed M9 to 2.5×10^4 cells/ml and various concentrations of chemically synthesized wild-type EDF were applied. Samples were incubated with rifampicin (10 μg/ml) as in Fig. 1A.

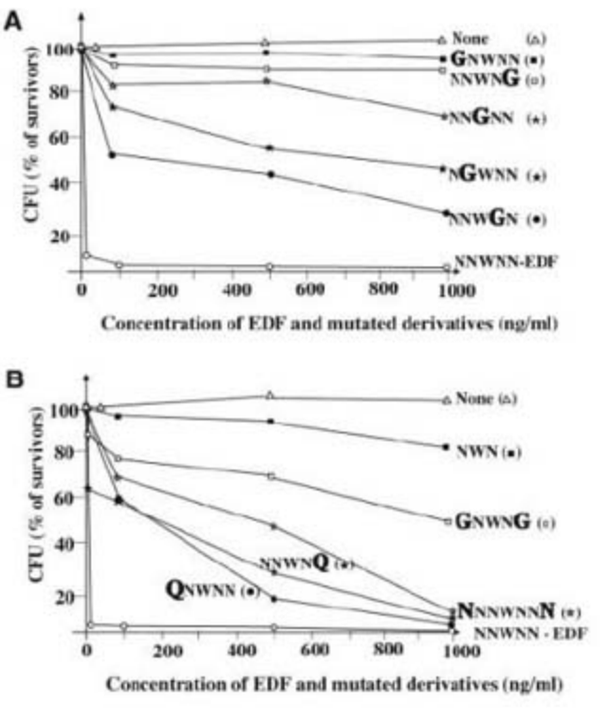

Fig. 4. NNWNN is the optimal molecule for EDF activity. (**A**) Each of the five amino acids is important for EDF activity. (**B**) The importance of size and external Asn residues for EDF activity. Chemically synthesized EDF (marked by NNWNN-EDF) or its modified derivatives were added at various concentrations to diluted cultures of *E. coli* MC4100*relA*$^+$. No EDF was added to a control culture (marked "None"). Samples were incubated with rifampicin as in Fig. 1A.

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Supporting Online Material

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Inactivation of the Interoceptive Insula Disrupts Drug Craving and Malaise Induced by Lithium

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Addiction profoundly alters motivational circuits so that drugs become powerful reinforcers of behavior. The interoceptive system continuously updates homeostatic and emotional information that are important elements in motivational decisions. We tested the idea that interoceptive information is essential in drug craving and in the behavioral signs of malaise. We inactivated the primary interoceptive cortex in amphetamine-experienced rats, which prevented the urge to seek amphetamine in a place preference task. Interoceptive insula inactivation also blunted the signs of malaise induced by acute lithium administration. Drug-seeking and malaise both induced Fos expression, a marker of neuronal activation, in the insula. We conclude that the insular cortex is a key structure in the perception of bodily needs that provides direction to motivated behaviors.

An important factor that contributes to drug-seeking in addicted individuals is the negative affective state that results from abstinence, described as increased anxiety, irritability, and sadness (*1*). Also important, at least at initial stages of addiction, are the bodily changes underlying the reinforcing properties of drugs. We hypothesized that affective states are monitored by the interoceptive system and particularly by the insular cortex, known to process homeostatic and emotional information (*2*, *3*). To test this idea, we reversibly inactivated the primary insular cortex in amphetamine-experienced rats and tested them with the place preference paradigm. We also injected naïve rats with malaise-inducing LiCl injections, monitored behavioral measures of malaise, and reversed those signs by inactivating the insula. A preliminary account has been presented (*4*).

Place preference tests (PPTs) used a two-compartment biased apparatus (*5*, *6*), with one white compartment paired with amphetamine (or saline) administration, connected by a brown alley to a black compartment paired with saline. Rats were placed in the connecting alley at the beginning of each 10-min session. The procedure took 30 days (Fig. 1A). Drug-naïve rats (all rats at PPT1, Fig. 1B) and rats treated with saline in the white compartment (fig. S1) spent more time in the black compartment, following their innate preference for darker places. Amphetamine-treated rats considerably increased the time spent in the white compartment on PPT2. One hour later, they received bilateral injections of a Na^+ channel blocker (2% lidocaine, 1 μl per side) that is effective to reversibly block cortical structures for about 20 min (*7*). Insular cortex inactivation changed the place preference back to the black compartment (Fig. 1B, PPT3) while producing no effects on general ambulation (fig. S2). The effect of insular cortex inactivation was reversible, because amphetamine-treated rats chose the white compartment on PPT4. The specificity of insular cortex inactivation was demonstrated by bilateral injections of lidocaine into the adjacent primary somatosensory cortex or by saline injection into the insular cortex of amphetamine-experienced rats. These rats significantly preferred the white compartment paired with amphetamine (Fig. 1B, PPT3). Amphetamine-experienced rats showed behavioral sensitization, a neural consequence of repeated psychostimulant exposure (fig. S3).

Place conditioning to amphetamine was paralleled by increased Fos immunoreactivity (Fos-ir), a marker of neuronal activation, in the insular cortex (Fig. 2, A and B). In contrast, the primary somatosensory cortex showed no significant activation in amphetamine-experienced compared with saline-treated rats (fig. S4). In addition, amphetamine-experienced rats showed increased Fos-ir in lateral hypothalamic area (LHA) orexin neurons 1 hour after PPT2, as previously demonstrated for cocaine and morphine (*8*) (Fig. 2, C and D).

If the inactivation of the insula disrupted the interoceptive feelings associated with drug clues, then its inactivation should also blunt the behavioral effects of a well-known malaise-inducing agent like LiCl (*9*). To test this idea, we bilaterally injected lidocaine into the insular cortex 5 min before administration of LiCl (0.15 M; 5 ml/kg intraperitoneally). Behavioral assessment started immediately and lasted for 30 min.

Rats injected with saline into the insular cortex or with lidocaine into the primary somatosensory cortex (Fig. 3) before the LiCl injection showed evident signs of malaise (*10*). They quickly laid on their bellies (Fig. 3, A and B), a postural index of malaise, dramatically decreased ambulation, and failed to respond with attentive movements when their cage was tapped. In contrast, the inactivation of the insular cortex blunted the behavioral consequences of LiCl administration (Fig. 3, A and B) for 15 min, a temporal course compatible with the inactivating effect of lidocaine at the dose we used (*7*).

To further evaluate the participation of the insular cortex in the responses to LiCl, we studied Fos-ir in a different group of rats killed 1 hour after LiCl or saline intraperitoneal injections. We found that LiCl administration induced a significant increase in Fos-ir in the anterior (bregma 0.95 to −0.51) insular cortex (Fig. 3C). In humans, the anterior insula is activated by the feeling of disgust induced by certain odors and during the observation of disgusted faces in others (*11*, *12*). Also, electrical stimulation of the insula frequently elicited upsetting gastrointestinal feelings, often associated with nausea (*13*).

The guide cannulae were aimed at the primary interoceptive cortex, located in the posterior granular insular cortex (*7*, *14*–*16*) (Fig. 4A). To confirm that we inactivated this cortical area, in addition to a cytoarchitectonic analysis of the cannulae tracks, we microinjected a different group of rats with the anterograde axonal tracer biotinylated dextran amine (BDA) or the retrograde tracer cholera toxin (CtB) into the same coordinates as the cannula placement (Fig. 4B). These tracer injections were restricted to the posterior granular insular cortex (*14*) and labeled axon terminals (BDA) or cell bodies (CtB) in the visceral thalamic nucleus, VPLpc, indicating that we were inactivating the primary interoceptive cortex (*15*). This interoceptive information is then distributed through more rostral and ventral insular cortices to prefrontal cortices, as well as to limbic structures (*17*, *18*).

Withdrawal symptoms vary a great deal across different drugs, but negative affect symptoms like anxiety, irritability, and sadness are common to all drugs (*1*). A recent study reported that patients with damage to the insular cortex could easily quit smoking because they lost the

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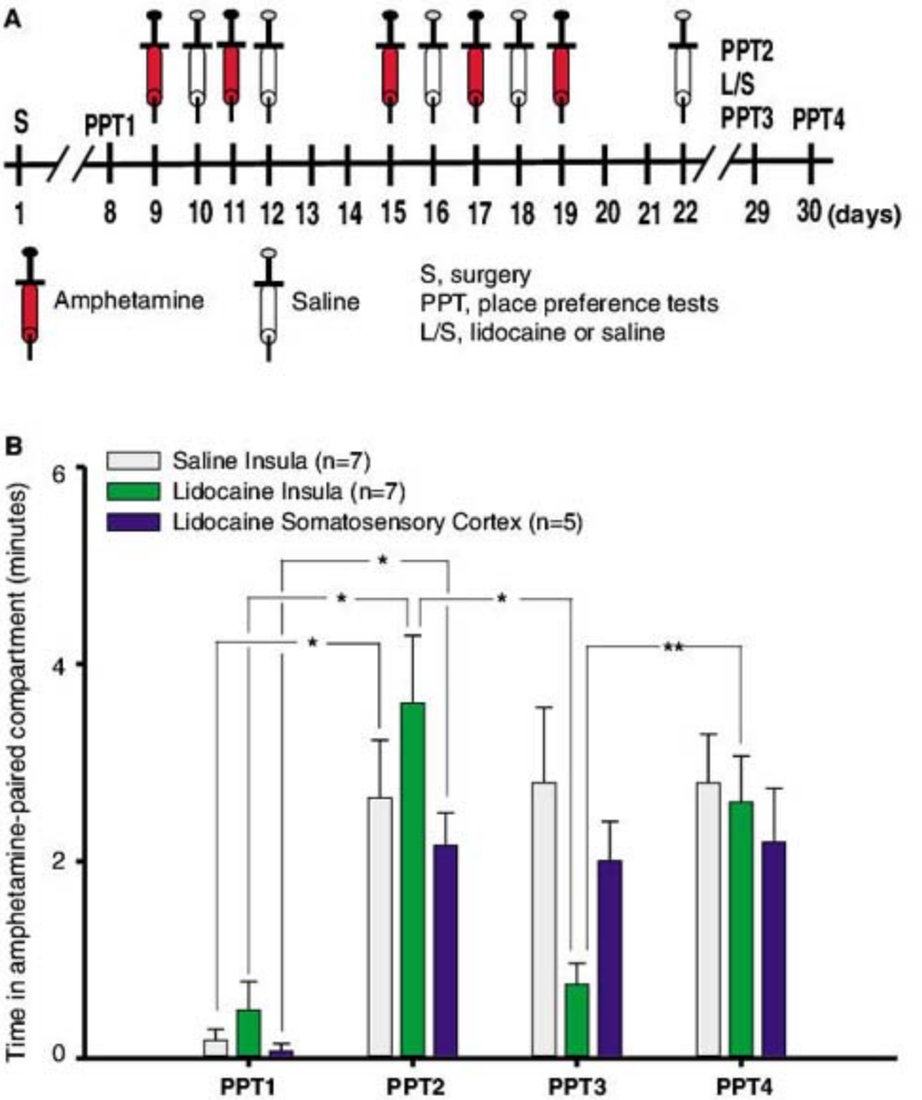

Fig. 1. Amphetamine-experienced rats changed their preference for the drug-paired (white) compartment in a place preference test (PPT) when the insular cortex was reversibly inactivated. (**A**) Time line of amphetamine administration and PPT. (**B**) Time spent in the drug-paired compartment during 10-min PPT sessions. Drug naïve rats strongly chose the black compartment (PPT1). After repeated amphetamine injections, all three groups were conditioned to prefer the white compartment (PPT2). One hour after PPT2, each rat was microinjected into either the primary somatosensory cortex or the insular cortex with lidocaine or saline in the insula 5 min before PPT3 began. Only rats microinjected with lidocaine in the insula reverted to preferring the default black compartment. The next day (PPT4), all groups chose the amphetamine-paired compartment. Single asterisks, $P < 0.001$; double asterisks, $P = 0.004$. Error bars indicate SEM; n is the number of rats.

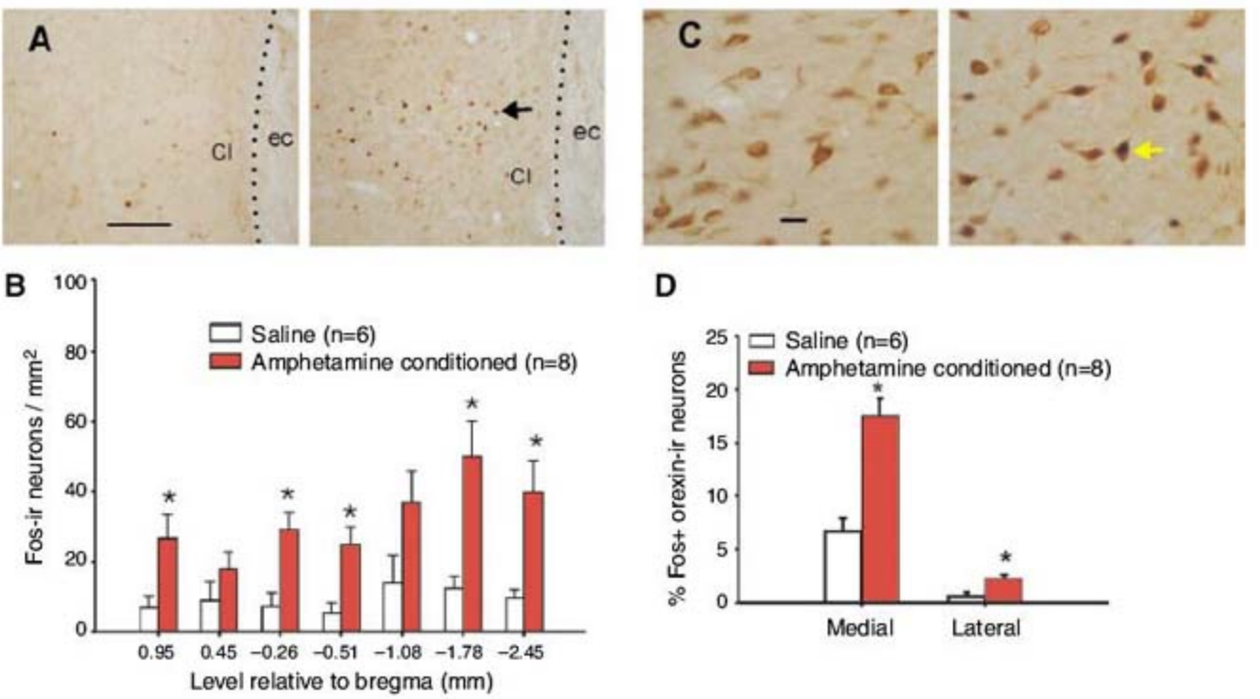

Fig. 2. Amphetamine-experienced rats had significant increases in Fos-ir in the insular cortex and in LHA orexin neurons after the PPT2. (**A**) Deep layers of the granular insular cortex showed near-absence of Fos-ir in a saline-treated rat (left) and significant increase in Fos-ir (arrow) in an amphetamine-experienced rat (right). (**B**) Quantification of Fos-ir in the granular insular cortex at different anteroposterior levels. Asterisks, $P < 0.042$. (**C**) Increased Fos-ir in LHA orexin neurons (arrow) in amphetamine-experienced rats (right) but not in saline controls (left). (**D**) Quantification of Fos-ir in orexin neurons. Note the stronger response of medial LHA neurons. Asterisks, $P = 0.001$ for the medial and $P = 0.011$ for the lateral LHA orexin neurons. Cl, claustrum; ec, external capsule; LHA, lateral hypothalamic area. Scale bars indicate 100 μm for (A) and 20 μm for (C).

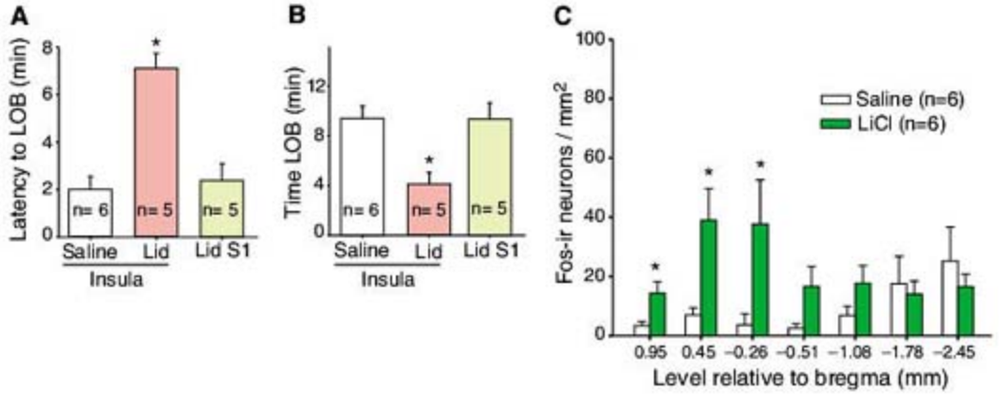

Fig. 3. Inactivation of the insular cortex attenuated malaise induced by LiCl. **(A)** Significant increase ($P = 0.002$) in the latency to lie on belly (LOB) and **(B)** in the time spent LOB ($P = 0.006$) of rats whose insular cortex was inactivated with lidocaine (Lid) compared with rats who received saline injection in the insula or lidocaine into the primary somatosensory cortex (S1). **(C)** LiCl intraperitoneal administration, but not saline, increased Fos-ir in rostral granular insular cortex. Asterisks, $P < 0.025$. Error bars indicate SEM.

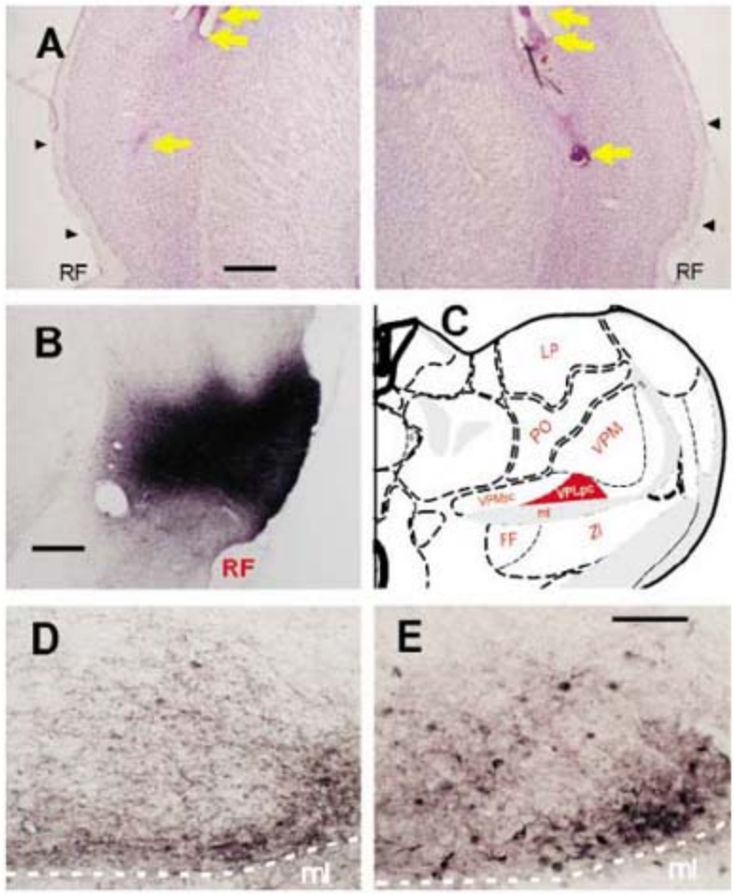

Fig. 4. Lidocaine injections targeted the posterior granular insular cortex. **(A)** Photomicrographs of a Nissl stained section showing the bilateral guide cannula (double arrows) and the injection cannula (single arrows) tracks, aimed at the posterior granular insular cortex (arrowheads). RF, rhinal fissure. **(B)** Photomicrograph of a BDA injection site into the posterior granular insular cortex, i.e., the same insular region inactivated with lidocaine. This small injection labeled axon terminals into the ventral posterolateral nucleus of the thalamus, parvicellular part [VPLpc, shown in red in (C)]. **(C)** Schematic drawing modified from Swanson's atlas (*7*) of the caudal thalamus. **(D)** Axon terminals and a few cell bodies in the VPLpc labeled from the granular insular cortex injection site in (B). Note the distribution of axons within the triangular VPLpc. **(E)** Photomicrograph of retrogradely labeled neuronal cell bodies into the VPLpc after an injection of CtB restricted to the posterior granular insular cortex. Scale bars are 0.5 mm for (A) and (B) and 100 μm for (D) and (E). Abbreviations: FF, fields of Forel; LP, lateral posterior nucleus; ml, medial lemniscus; PO, posterior complex; VPM, ventral posteromedial nucleus; VPMpc, ventral posteromedial nucleus parvicellular part; ZI, zona incerta.

urge to smoke (*19*). The role of this cortex in drug craving is also supported by several imaging studies showing activation of the insula, as well as other cortical and subcortical regions, in addicts with cue-induced drug craving (*20*–*22*). Remarkably, activation of the insular cortex was positively correlated with subjective reports of drug craving (*20*).

The conscious perception of interoceptive signals may be a general role of the insular cortex that explains why its inactivation blunts the urge to get a drug in addicted persons. It remains to be determined whether the insula anticipates the hedonic properties of the drug or whether the insula reports the aversive state associated with withdrawal that could be alleviated by amphetamine, as if it were a medicine. As J. Garcia has shown and discussed (*9*), when a flavored liquid like milk or grapefruit is given to animals recovering from malaise (induced for instance by LiCl), they will seek the flavor that is now predictive of a medicine. The insula is the cortical region that likely underlies conscious perception of the physiological state of the body (*23*), and it is in a key position to distribute this information to orbital, medial, and cingulate prefrontal cortices involved in decision-making (*24*) and to limbic structures involved in emotional responses (*17*, *25*). Interoceptive perception is modulated by attention (*26*), and, like exteroceptive systems, the insular cortex and the interoceptive thalamus (VPLpc) are connected to a particular sector of the thalamic reticular nucleus, a key structure in selective attention (*16*).

Damage to the insular cortex blocked the behavioral expression of a conditioned taste aversion (*27*, *28*), and, as shown here, its reversible inactivation blunted the behavioral responses to an unconditioned stimulus (LiCl) that induced malaise. Patients with insular cortex damage reported no decrease in food intake or desire to eat and no less pleasure in eating (*19*). These findings suggest that the insular cortex is reporting strong deviations from a "well being state," and if so then a low or absent insular cortex activity is interpreted by the brain as "feeling sound." However, insula activation has also been reported in relation to pleasant touch sensations or sexual arousal (*2*). Interestingly, whereas exposure to appetitive food stimuli increased the metabolism of many brain regions including the insula, only the activation of the right orbitofrontal cortex, but not the insula, was correlated with self-reports of hunger and desire for food (*29*).

Our results indicate a key role for the interoceptive insular cortex in the craving for drug in amphetamine-experienced animals and in the perception of malaise induced by lithium administration. Our results further suggest that the modulation of insula activity using noninvasive approaches (*30*) should be considered as a therapeutic target to alleviate the craving for drugs of abuse, as recently proposed by Bechara and colleagues (*19*) for nicotine craving, and, in a more general sense, to ease distressful interoceptive symptoms not related to drug craving.

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Please visit the following websites for information about the Biology Department **(website: http://www.bu.edu/biology/)** and the interdepartmental Program in Neuroscience **(website: http://www.bu.edu/neuro/)** at Boston University.

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Gladstone Institute of Neurological Disease
1650 Owens Street
San Francisco, CA 94158
E-mail: lmucke@gladstone.ucsf.edu
Website: http://gladstone.ucsf.edu/gind

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The Department of Biology at William Paterson University invites applications for two tenure-track faculty positions at the **ASSISTANT PROFESSOR** level. Ph.D. required. Postdoctoral research and teaching experience preferred. Candidates are expected to develop a research program involving students and taking advantage of facilities, including an existing mouse facility (which has a full-time technician and no cage charges), electron microscopy suites and well-equipped molecular biology laboratories. The Department offers B.S. and M.S. degrees in both biology and biotechnology. Teaching responsibilities for both positions will include some combination of graduate, undergraduate, and service or general education courses.

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FROM PROTONS TO POETRY

Neurological and psychiatric disorders affect a growing number of individuals—nearly one in five Americans in a given year and more than two billion people worldwide. Furthermore, the scope of neuroscience is vast—ranging from the most basic cellular-level research to translational medicine—and many unanswered questions remain. Interesting niche areas have emerged in neuroscience research such as neuroeconomics, neuromarketing, and neural networks. Together, these factors make neuroscience one of the more exciting and opportunity-laden fields in which to pursue a scientific career. **By Emma Hitt**

The subject areas that qualify as neuroscience are as far-reaching and as interconnected as neurons themselves. Consequently, neuroscientists often work on questions that span several distinct subfields. Many neuroscience programs are interdepartmental and take on the structure of an institute rather than a department. For example, the mission at the Neuroscience Institute of Stanford is to "achieve a new synthesis from molecules to mind, from analysis to application, from science to society." According to director **William Mobley,** the goal is to translate the science "all the way from looking at synaptic function to deciding how children can learn how to read more effectively." The institute includes 150 faculty participants from the Schools of Medicine, Humanities and Sciences, Engineering, Education, Law, and Business.

Likewise, the Harvard Center for Neurodegeneration and Repair resides in small areas of many buildings and labs rather than being confined to one building. "The center has affiliations with 18 hospitals, and whenever we set ourself a new research challenge, we identify the very best people in the community and draw them into a new collaborative program," says **Adrian Ivinson,** the center's director. "That's very different from the approach in usual principal investigator–based labs." To answer questions about complex neurological diseases such as Alzheimer's and multiple sclerosis, one needs biostatisticians, disease experts, clinical experts, high throughput genotyping capacity, databases and databanks, and "you need them at a level that you couldn't expect to find in one lab," he says.

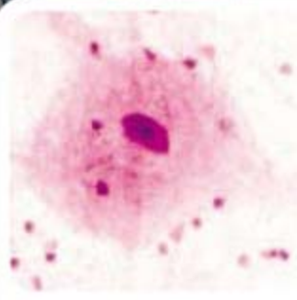
At Berkeley, the Helen Wills Neuroscience Institute has four main divisions: cellular and molecular, developmental, systems and computational, and cognitive and behavioral. According to **John Flannery,** the acting director, the institute has 50 faculty distributed across the campus, conducting research from the cellular level all the way up to dealing with patients. "Graduates from our group can not only go to a basic science department, they could go to a medical school clinical department, and there's a lot of interest in pharmaceuticals and biotechnology, especially in the Bay area," says Flannery.

Translational Cures

Research likely to garner the most financial support will be that which has clinical applications, collectively called translational research. Psychiatric disorders are in fact brain disorders that involve abnormal activity in brain circuits, so having researchers who understand the brain in a deep and integrated way is going to be critical for the future, says **Thomas Insel,** director of the US National Institute of Mental Health (NIMH). "We need to have people who are interested in these illnesses and yet also are skilled in neuroscience. Neuroscience M.D.-Ph.D.s and Ph.D.s are definitely an important cohort for increasing NIMH support," he adds.

"The evidence keeps coming that there are genetic causes or risk factors for most if not all neurological diseases," notes **Lars Olsen,** past chair of the Department of Neuroscience, at the Karolinska Institutet in Stockholm, Sweden. "A striking example is Parkinson's disease—we know for sure that some forms are directly inherited and that complex genetic risk factors appear important for the rest of the cases." According to Olsen, a trend in academia and industry will be to establish that Parkinson's disease for example, is not continued »

> "Having researchers who understand the brain in a deep and integrated way is going to be critical for the future."



From top: **Michael Lehman,** chair of the Department of Anatomy and Cell Biology at the University of Western Ontario with students; **Thomas Insel,** director of the US National Institute of Mental Health; **Glenda Halliday** and student **Christine Song.**

UPCOMING FEATURES

Focus on Diversity — November 16

Interdisciplinary Research — November 23

one disease, but perhaps 10, and to develop individualized treatments based on understanding of etiology.

Programs tailored to translational research are springing up nationwide in part due to initiatives in translational research put forth by the US National Institutes of Health (NIH), notably, the NIH's Blueprint for Neuroscience Research. The Blueprint is a cooperative effort among 16 NIH institutes, centers, and offices that supports the development of new tools, training opportunities, and other resources to assist neuroscientists in both basic and clinical research.

Funding increases are needed "to ensure that our best and brightest young people will enter the field and continue to make neuroscience research advances."

–David Van Essen

Most of the major medical schools now have translational research programs, says **Raquel Gur,** the director of the neurotherapeutics program at the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania. "Translational research is really the call of the hour," she says. According to Gur, whose program specializes in schizophrenia, translational neuroscience requires thoughtful consideration of the relevance of basic research findings to human behavior. "Until we started our translational research efforts, basic and clinical scientists read different journals, and now they are e-mailing each other relevant articles."

Gur advises graduate students and junior postdocs in the neurosciences to push themselves to get what they need from their program or school rather than just accepting the resources available. "Ask yourself how you can become part of an interdisciplinary team that works toward a higher goal," she advises.

Going Global

Opportunities exist globally in the neurosciences. Neural engineering and psychoneuroimmunology are areas of increasing interest in Australian neuroscience research, according to **Glenda Halliday,** president of the Australian Neuroscience Society. Other areas that are emerging include neural stem cell research, neuroinformatics, and computational neuroscience, she says.

At the Karolinska Institutet, areas of research include spinal cord injury and repair, the role of the dopamine system in health and disease, neurotrophic factors and their receptors, the synapse and vesicle recycling, and neuronal membrane receptors and receptor interaction. "Previously, almost all neuroscience Ph.D. students at Karolinska were recruited from classes of students studying to become M.D.s," says Olsen "but in the last 10–15 years this has changed so that now a small minority of the students we accept for our Ph.D. program are derived from the M.D. curriculum classes."

Show Me the Money

By most accounts, the limited funds for the hiring of postdocs and junior faculty make such positions competitive, and this holds true for the neurosciences. "It's difficult right now because the NIH budget is not keeping pace with the increasing expense of biomedical research," says Berkeley's Flannery. "Private universities such as Harvard, Yale, and Princeton have historically hired more at senior levels—tending to hire the most distinguished scholars they could find. Junior faculty would be hired for three to six years and then have to move elsewhere, although there is a trend to hire more junior faculty now, and this includes an effort to recruit more women and minorities into the sciences." (Find more on this trend in the careers feature published September 14, 2007 – "Make Way for the Next Generation: Junior Faculty Are Moving In" – dx.doi.org/10.1126/science.opms.r0700038.)

The total NIMH budget for 2007 is $1.4 billion, a figure that has remained essentially flat since 2004. Approximately 3,000 grants for a total of $1.405 billion are projected to be funded by the NIMH in fiscal year 2008. Similarly, the US National Institute of Neurological Disorders and Stroke (NINDS) funding has also remained consistent at $1.533, $1.534, and $1.537 billion in 2006, 2007, and 2008, respectively. Current supported funding areas at NINDS and NIMH include counterterrorism and neuroscience research, neural prosthesis program, neural stem cells, adult and pediatric translational research and treatment development, and the NIH neuroscience Blueprint.

"Some institutions [in the United States] are no longer recruiting junior-level faculty who don't have their own grant support," says **Michael Lehman,** chair of the Department of Anatomy and Cell Biology at the University of Western Ontario and president-elect of the Association for Neuroscience Departments and Programs (ANDP). "It's a somewhat dismal environment for recruiting young scientists," he adds. "If only established investigators continue to be funded there will be a generational gap, and that's bad for neuroscience and science in general."

continued »

Association for Neuroscience Departments and Programs (ANDP)
www.andp.org

Australian Neuroscience Society
www.ans.org.au

Department of Anatomy and Cell Biology, University of Western Ontario
www.uwo.ca/anatomy

Harvard Center for Neurodegeneration and Repair
www.hcnr.med.harvard.edu

Helen Wills Neuroscience Institute, Berkeley
neuroscience.berkeley.edu

Institute for Translational Medicine and Therapeutics, University of Pennsylvania
www.itmat.upenn.edu

Karolinska Institutet, Department of Neuroscience
www.neuro.ki.se

NeuroInsights
www.neuroinsights.com

Neuroscience Institute of Stanford
neuroscience.stanford.edu

Neurotechnology Industry Organization
www.neurotechindustry.org

Society for Neuroscience (SfN)
www.sfn.org

US National Institutes of Health (NIH)
www.nih.gov

US National Institute of Mental Health (NIMH)
www.nimh.nih.gov

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BROWN

Tenure-Track Position in Neuroscience

The Department of Neuroscience of the Warren Alpert Medical School at Brown University invites applications for a tenure-track position at the level of Assistant or Associate Professor. Applicants should have a Ph.D. or M.D. degree, postdoctoral research experience, and a record of excellent research that addresses fundamental questions in neuroscience. We seek individuals who are using innovative techniques to explore neural mechanisms bridging molecular, neuronal, and brain functions. The successful applicant must be qualified to develop an externally funded research program, and must be committed to the education of undergraduate, graduate, and medical students. The programs in neuroscience at Brown are in the process of expanding and the Department moved to a new building in early 2007. For more information about the environment, see **http://neuroscience.brown.edu/** and **http://www.brainscience.brown.edu/**.

Applicants should submit a curriculum vitae, description of research plans and no more than 3 representative reprints electronically to **neurosearch@brown.edu**. Letters of recommendation (3 for Assistant and 5 for Associate Professor) should be sent to: **Search Committee Chair, Department of Neuroscience, Box GL-N, Brown University, Providence, RI 02912**. Applications received by **December 1, 2007** will be ensured full consideration.

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Faculty Position in Systems Neuroscience

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Department of Anatomy & Neurobiology

We seek an individual whose research uses non-human primates to address important questions in systems neuroscience for a tenure track faculty position at a junior or senior level in the Department of Anatomy and Neurobiology at Washington University School of Medicine in St. Louis (**http://thalamus.wustl.edu**). Applicants who work on sensory processing and whose research includes a strong computational aspect are especially encouraged to apply. The department houses 25 faculty actively involved in neurobiological research, and it is part of a much larger interdepartmental neuroscience program (**http://neuroscience.wustl.edu**) that includes the Cognitive, Computational, and Systems Neuroscience (CCSN) pathway. Excellent laboratory space is available in a state-of-the-art primate facility.

To apply send an email attachment of one PDF file (10 page limit) to **susan@brainvis.wustl.edu** (include cover letter, CV, research summary, and names/email addresses of three references). Also, arrange for three reference letters to be sent to **Dr. David Van Essen**, by email to **susan@brainvis.wustl.edu**. Applications and letters must be received by **December 1, 2007**.

AA/EOE M/F/D/V.

University of Victoria

Assistant or Associate Professor Tenure-Track Position

The Division of Medical Sciences at the University of Victoria, in partnership with the University of British Columbia, invites applications for a full-time tenure-track faculty position in Neuroscience at the rank of Assistant or Associate Professor. A demonstrated research potential and a commitment to establishing a successful research program are required. Primary responsibilities of the successful candidate will be to support the Island Medical Program and its medical students through curriculum planning, classroom and laboratory teaching, and student mentoring and assessment. Applicants should possess a M.D. and/or Ph.D. with demonstrated experience in teaching.

The primary appointment for this position will be to the Division of Medical Sciences at the University of Victoria, with an affiliate appointment to the Faculty of Medicine at UBC. Further information about the Island Medical Program can be obtained at **http://web.uvic.ca/imp** Applications should include an up to date CV, teaching dossier and research plan, and the names of three referees. These can be emailed or sent directly to:

Oscar G. Casiro, MD, FRCPC
Associate Dean, Island Medical Program
University of British Columbia
Head, Division of Medical Sciences
University of Victoria
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University of Maryland, College Park Program in Neuroscience and Cognitive Science

Computational Neuroscience – Tenure-track faculty

The Neuroscience and Cognitive Science program (NACS) at the University of Maryland is seeking a new tenure-track faculty member, at the assistant professor level. Computational neuroscientists working in any areas including sensory and motor physiology, analysis of control systems, and cognitive neuroscience will be considered. The successful candidate will hold a joint appointment in both the NACS Program and an academic department depending on the research interests of the faculty member. This may be in Biology, Computer Science, Electrical and Computer Engineering, Hearing and Speech Sciences, Kinesiology, Linguistics, or Psychology. NACS is a tightly integrated community of scholars focused on aspects of neuroscience and cognitive science. Many faculty enjoy productive research collaborations with scientists in the Washington DC area.

- **Responsibilities:** Candidates will be expected to develop a vigorous extramurally funded research program. Teaching duties will include a graduate-level course in computational neuroscience, as well as undergraduate/graduate courses to be determined by the tenure-track department. Duties will also include student advising and administration as determined by the Director of NACS and the department of tenure.
- **Qualifications:** An earned doctorate in a discipline relevant to the candidate's field of teaching and research is required. Candidates who integrate theoretical with experimental research are preferred. We seek candidates with demonstrated teaching and research excellence capable of maintaining an extramurally funded research program. NACS details: **www.nacs.umd.edu**.
- **Salary:** Commensurate with qualifications and experience.
- **Position available:** Earliest start date is fall semester 2008.

Applications: For best consideration send, by **December 15, 2007**, a CV, names and addresses (including emails) of three possible references, and statements of both research interests (documenting extramural funding) and teaching interests to **NACS Search, NACS Program, 2131 Biol/Psyc Building, University of Maryland, College Park, MD 20742**.

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It is not all doom and gloom, however, as scientists are being increasingly vocal about the funding shortfall. Earlier this year **David Van Essen,** president of the Society for Neuroscience (SfN), strongly urged the US House and Senate appropriations subcommittees on labor, health and human services as well as on education to increase NIH funding by 6.7 percent per year for each of the next three fiscal years, stating that this is needed "to ensure that our best and brightest young people will enter the field and continue to make neuroscience research advances."

Table 1. Select Emerging Multidisciplinary Fields in the Neurosciences

Computational Neuroscience	Combines traditional neuroscience with computer science.
Neural Engineering	Uses engineering techniques to investigate the function and manipulate the behavior of the central or peripheral nervous systems.
Neural Networks	The application of neuroscientific studies of the structure and function of the human brain in machine information processing and decision making.
Neuroeconomics	Combines neuroscience, economics, and psychology to study how we make decisions.
Neuroergonomics	The matching of technology with neurologic capabilities to achieve safe working conditions.
Neuroesthetics	Understanding the esthetics of art and music at the neurological level.
Neuroethics	The ethics of neuroscience and neurotechnology research.
Neurolinguistics	The science concerned with the neural mechanisms underlying the comprehension, production, and abstract knowledge of language.
Neurophilosophy	Investigation of philosophical theories in relation to neuroscientific hypotheses, dealing with philosophical problems of the cognitive neurosciences and addressing questions about cognition and consciousness, and what the neural correlates of human consciousness may be.
Psychometrics	The theory and technique of educational and psychological measurement.

On the industry side, venture capital investment in new and emerging neurotechnology companies reached a record high in 2006, increasing 7.5 percent to $1.67 billion, according to the Neurotechnology Industry 2007 Report, produced by NeuroInsights. Approximately one in four venture dollars now invested in life science companies in the United States goes to companies focused on the brain and nervous system, which represents a more than threefold increase since 1999, according to the NeuroInsights report. In 2006, the neurotechnology industry comprised over 500 companies, developing drugs, devices and diagnostics for the brain and nervous system, generating worldwide revenues of $120.5 billion.

"I think people seeking a career in neuroscience need to be hopeful," says Mobley. "My postdocs express concern about whether or not they will get funding and be able to pursue a career, but it's important to remember that there are many possible ways to do great thinking and great science," he says. "They need to find those pieces of the puzzle that fit them best and they should not give up hope."

The Leaky Pipeline

As in other areas of science, women still have some catching up to do with regard to reaching the higher echelons of academia. The ANDP assesses neuroscience training, primarily in North America, and conducts a National Survey of Neuroscience Programs. The last ANDP survey was conducted in 2005, and a subsequent survey was scheduled to be sent out to member programs early this fall. The 2005 report included responses from 88 of the 140 graduate training programs that were members of the ANDP and indicated that women comprise more than 60 percent of the graduate students in neuroscience but approximately 25 percent of tenure-track faculty, a number that has changed little since 1998. Furthermore, the percentage of full professors who are women remains a low 21 percent.

The demands of life outside of a professional scientific career and the conscious or unconscious biases that exist can make it harder for women to advance. "All of these are active areas of discussion, not just in neuroscience, but in biomedical science over all," Lehman says.

Van Essen, with the SfN, notes that one of his society's key interests is to encourage diversity in terms of increasing the number of both women and minorities coming into and succeeding at each stage of the pipeline. "Having successful role models [for upcoming scientists] is important," he says.

Strategic Career Planning

Neuroscience has a flexibility in that it can be combined with a multitude of disciplines (Table 1), so an effort should be made to diversify skills while keeping in mind one's career interests. For example, postdocs might benefit from getting an MBA, a computer science degree, or an economics degree to complement their conventional neuroscience training.

"Neuroscience training has many varied and productive career options for students," Lehman says. "That's in contrast to the traditional path of entering a medical school environment and depending on grant support. There are so many other types of career paths in which students can be happy, successful, and productive."

Likewise, Van Essen recommends getting broad training, "not just in one narrow area of neuroscience, but trying to obtain a background that uses multiple approaches and can attack problems from a relatively broad perspective."

A strong demand exists for people with regulatory and clinical trial management expertise related to neurological diseases and psychiatric illnesses, notes **Zack Lynch,** executive director, with the Neurotechnology Industry Organization.

Whatever path a student decides upon, neuroscience is replete with opportunities for graduate students and postdocs who have given thought to planning their career path. People who are just entering into this field will be the Nobel Prize winners of this next generation, says Insel. "This really is the place for the brightest and the best students to jump in because we know so little, and the opportunities are so great."

Emma Hitt is a freelance medical and science writer residing in Marietta, Georgia.

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Southern Illinois University School of Medicine

Assistant Professor, Anatomy
Southern Illinois University, Carbondale

The Department of Anatomy at Southern Illinois University School of Medicine-Carbondale invites applications for a tenure-track faculty position at the Assistant Professor level. Qualified candidates must have a Ph.D., M.D., or equivalent degree, at least two years of postdoctoral experience, and ability to perform productive independent research. Opportunities for collaboration exist within several basic science and clinical departments, with existing strengths in neuroscience, reproduction, cancer, cell and molecular biology, and medical education. Teaching experience or training in the anatomical sciences (histology/cell biology, gross anatomy, embryology, or neuroanatomy) is preferred. The medical curriculum is case-based and small group oriented. This is a 12-month, state-funded position with a competitive salary, substantial startup package, and spacious lab facilities. Carbondale is located two hours southeast of St. Louis and borders the Shawnee National Forest. The community enjoys scenic getaways, abundant outdoor recreation, a vibrant university with a growing research culture, and an array of local attractions. This is a security-sensitive position. Before any offer of employment is made, the University will conduct a pre-employment investigation, which includes a criminal background check.

Review of applications will begin **December 1, 2007** and will continue until the position is filled. Applicants should provide a letter of introduction, a curriculum vitae that includes descriptions of research plans and teaching interests, and should have three letters of reference sent to:

Search Committee, Department of Anatomy
School of Medicine
Mail Code 6523
Southern Illinois University Carbondale
1135 Lincoln Drive
Carbondale, IL 62901

SIUC is an Affirmative Action/Equal Opportunity Employer that strives to enhance its ability to develop a diverse faculty and staff and to increase its potential to serve a diverse student population. All applicants are welcomed and encouraged and will receive equal consideration.

CHILDREN'S HOSPITAL BOSTON
HARVARD MEDICAL SCHOOL

Assistant/Associate Professor
Department of Otolaryngology and Neurobiology Program

The Department of Otolaryngology at Children's Hospital Boston, in collaboration with the Neurobiology Program, seeks applications to fill a full-time tenure-track Assistant/Associate Professor position. The successful candidate will hold either a PhD and/or MD degree and will join the interactive neuroscience community at Children's Hospital and Harvard Medical School. We seek an outstanding scientist that will establish a vigorous research program in neuroscience related to otolaryngology. Areas of interest include development, cell and molecular biology and physiology of the auditory and vestibular systems. Modern laboratory space will be located in the new Children's Hospital Center for Life Science Building to be opened in the Spring of 2008. The investigator will hold both Children's Hospital Boston and Harvard Medical School faculty appointments.

Please submit a current CV, a two- or three-page description of research interests and directions, and three to five reference letters. Materials should be sent by **January 15, 2008** to: **ORLjob@childrens.harvard.edu, c/o Gabriel Corfas, Ph.D., Chair ORL Search Committee.**

For more information about the Neurobiology Program at CHB see:

http://www.childrenshospital.org/research/mult_progs/

Equal Opportunity/Affirmative Action Employer.

JOHNS HOPKINS
MEDICINE
SCHOOL OF MEDICINE

Faculty Positions
The Solomon H. Snyder
DEPARTMENT OF NEUROSCIENCE

Applications are invited for tenure-track faculty positions at both junior and senior levels in the Solomon H. Snyder Department of Neuroscience at the Johns Hopkins University School of Medicine. Applicants should have interests in molecular, cellular, developmental, systems or behavioral neuroscience, a Ph.D. or M.D., and a strong record of research accomplishments. Faculty members are expected to have, or establish, creative independent research programs and participate in teaching graduate and medical students. Deadline for applications is **November 30, 2007**. The Johns Hopkins University is committed to enhancing the diversity of its faculty and encourages applications from women and minorities.

Please submit a PDF file containing curriculum vitae, names and contacts for three references and a brief description of current and future research interests.

Richard L. Huganir, Ph.D.
Search Committee
Department of Neuroscience
The Johns Hopkins University
School of Medicine
725 North Wolfe Street, PCTB 904
Baltimore, Maryland 21205

JHUNeuroscience@jhmi.edu

An EEO/AA Employer.

Southern Illinois University Carbondale

DIRECTOR
Center for Integrated Research in Cognitive and Neural Sciences
http://www.siu.edu/~ovcr/circns.html

Southern Illinois University Carbondale (SIUC) invites applications for the Director of a new Center for Integrated Research in Cognitive and Neural Sciences (CIR-CNS), an interdisciplinary initiative that will build on existing researchers on the SIUC and SIU School of Medicine Springfield campuses. The Director will have a unique opportunity to establish/promote multidisciplinary research groups in fundamental, integrative, rehabilitative, and behavioral neural science. The Director will be offered a 12-mo tenure-track appt. (Prof./Assoc. Prof.) in the dept. most appropriate to the candidate's expertise, among the Depts. of Anatomy, Physiology, or Biochemistry & Molecular Biology at SIU School of Medicine-Carbondale, or the Dept. of Psychology or Rehabilitation Institute at SIUC.

Requirements: Ph.D. and/or M.D., strong publication record, experience with multidisciplinary research groups, and successful training of graduate and/or postdoc students. The ideal candidate should have an internationally recognized and funded research program in an area of basic and/or clinical neuroscience, and leadership qualities to promote collaboration and ensure vigorous growth of the Center in the full range of cognitive and neural sciences.

Review of applications will begin **November 30, 2007**, and continue until the position is filled. Applicants should submit a cover letter, c.v., research summary, and contact information for 4 references (PDF format) to: **lsmartin@siu.edu**, or mail to: **CIR-CNS Search Committee, Office of the Vice Chancellor for Research & Graduate Dean, Anthony Hall Room 220 Mail Code 4344, SIUC, 1265 Lincoln Dr., Carbondale, IL 62901.**

This is a security-sensitive position: before any offer of employment is made, the University will conduct a pre-employment background investigation, which includes a criminal background check. SIUC is an Affirmative Action/Equal Opportunity Employer that strives to enhance its ability to develop a diverse faculty and staff to increase its potential to serve a diverse student population. Women and minority applicants are encouraged to apply. All applications are welcomed and encouraged and will receive consideration.

CEDARS-SINAI

Exceptional Career Opportunities Research Technicians and Postdoctoral Fellows

The newly formed Heart Institute at Cedars-Sinai Medical Center in Los Angeles, California is poised to become a national leader in the development of novel treatments for heart disease. CSMC is already a leader in translational medicine, where bench to bedside can become a reality. As our research program is undergoing substantial growth, we are looking for several outstanding and motivated people to join our team. Current opportunities include:

Molecular Biology Technician
- BS/MS in biology or chemistry
- 5+ years vector/cloning experience
- Strong organizational skills (i.e. freezer mgmt)
- Experience in lab management preferred

Animal Technician
- BS/MS in biology or chemistry
- 5+ years experience in:
  - Small/large animal surgery (mouse preferable)
  - Aseptic technique
  - Familiar with AALAC principles
  - Able to assist lab personnel in a variety of animal studies

Tissue Culture Technician
- BS in biology, chemistry or physics
- 2+ years experience
- Able to perform routine purification and maintenance of mammalian heart cells and/or cell lines in culture.
- Contributes to general maintenance of the laboratory, equipment and supplies.
- Demonstrated ability to use sterile technique

Protein Biochemistry Technician
- BS/MS in biology or chemistry
- 2+ years experience in protein chemistry
- Able to perform and instruct in
  - Protein biochemistry techniques including
    - Purification and quantitative/qualitative analyses
    - 2D gel electrophoresis
    - Maintain lab stocks of buffers and reagents
- Experience in proteomics lab preferred

Postdoctoral Fellows
- MD and/or PhD
- Background in physiology, bioengineering or molecular biology
- Meaningful commitment to academic trajectory in cardiobiology

Join an exceptional team of scientists, faculty, researchers and staff who are leaders in basic and clinical cardiac research. Cedars-Sinai, a tertiary acute care academic medical center affiliated with the David Geffen School of Medicine at the University of California, Los Angeles is committed to excellence in compassionate patient care, research and community programs to improve the lives of our patients. Cedars-Sinai is proud to be on the list of "America's Best Hospitals," as ranked by *U.S. News and World Report.*

Please submit CV's to: **Patricia Carson, Academic Human Resources, Cedars-Sinai Medical Center, carsonp@cshs.org or mail to: 8711 West 3rd Street, Los Angeles, CA 90048.**

UTMB
The University of Texas Medical Branch

FACULTY POSITION IN NEUROPHARMACOLOGY ASSISTANT OR ASSOCIATE PROFESSOR Department of Pharmacology and Toxicology The University of Texas Medical Branch (UTMB)

A tenure track Assistant or Associate Professor position is available in the Department of Pharmacology and Toxicology at UTMB. We seek candidates with proven research and teaching skills in neuropharmacology or related areas. Associate Professor candidates should demonstrate an established research program and evidence of sustained extramural funding. Preference will be given to candidates interested in working in a highly collaborative, interdisciplinary environment with interests complementing those of departmental and center faculty. The Department of Pharmacology and Toxicology [**www.utmb.edu/phtox/**] is comprised of 16 tenure track faculty who apply contemporary molecular, cellular, chemical, and behavioral approaches to the study of addiction, psychiatric disorders, cancer, cell signaling, gene regulation, drug metabolism, molecular toxicology and the structure and function of biologically active molecules. Opportunities for interaction with several translational research centers are excellent, including the Center for Addiction Research [**http://www.utmb.edu/addiction**] focused on new targets and therapeutic options for addiction treatment, and the Program in Chemical Biology, which employs combinatorial and synthetic organic chemistry in pursuit of novel reagents for biomedical research. The position offers a competitive salary and benefits package.

All applications should contain the following materials: current curriculum vitae, statement of research accomplishments and future plans (no more than three pages), names and contact information of three references. Please submit to: **Dr. Kathryn A. Cunningham, Vice Chair, Department of Pharmacology and Toxicology and Director of the Center for Addiction Research, The University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-1031.** You may contact us by email via **Ms. T.L. Landry** at **tllandry@utmb.edu.**

UTMB is an Equal Opportunity, Affirmative Action Institution which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

Faculty Positions in Neuromodulation Medical School, University of Minnesota

The University of Minnesota Medical School, its newly founded Institute of Translational Neuroscience, and its partner, University of Minnesota Physicians seek to hire faculty in the research area of Neuromodulation.

1) Director of Neuromodulation: The successful applicant will be a midcareer clinician investigator with rank and tenure status dependent on qualifications who can direct an integrated clinical neuromodulation program being developed by the departments of Neurology, Neurosurgery and Psychiatry in conjunction with the practice plan. Appointment is possible in any of the clinical neuroscience departments, i.e. Neurology, Neurosurgery, and Psychiatry, according to the individual's background and interests. The collaborating departments share a single administrative center. The successful applicant is expected to have clinical experience as well as an established research program that uses neuromodulation to treat diseases/disorders of the nervous system.

2) Professor of Neuromodulation: The successful applicant will be a physician-translational neuroscientist at the Assistant, Associate, or Full Professor level in the tenure track who is expected to have an established research program that uses neuromodulation to treat diseases/disorders of the nervous system. Appointment is possible in any of the clinical neuroscience departments and/or Department of Neuroscience.

3) Professor and Director of Neuromodulation: For an individual with the necessary interests and experience, combining the positions may be possible and appropriate.

For both positions, a record of ongoing extramural funding in the field is desirable. Areas of interest include but are not limited to degenerative diseases, movement disorders, dementia, depression, psychiatric disorders, developmental disorders, epilepsy, pain. These recruitments are supported by the practice plan, Medical School, and University's Institute of Translational Neuroscience. As one of the largest research universities in the country, the University of Minnesota offers a rich environment in basic, translational, and clinical neuroscience research, and a long tradition of collaborative interactions. The University of Minnesota in Minneapolis is located on an urban campus which overlooks the Mississippi River and which houses many colleges in addition to the Medical School and Academic Health Center. Starting date is negotiable. Salary and start-up funds will be competitive and commensurate with education and experience. Candidates must have an M.D. degree or a combined M.D./Ph.D. degree and must be a U.S. citizen or be able to secure permanent resident status.

Applicants should send a current curriculum vitae, statement of research interests and intentions, and three letters of reference to: **Neuromodulation Search Committee, Attention: Walter C. Low, Ph.D., Chair, Search Committee, Department of Neurosurgery, University of Minnesota, 2001 Sixth Street SE, Minneapolis, MN 55455 USA** or **lowwalt@umn.edu.** Electronic versions of the required information may be e-mailed but must be followed with a hard-copy for the official search files. Review of applications will continue until positions are filled.

The University of Minnesota is an Equal Opportunity Educator and Employer.

CAREERS IN NEUROSCIENCE

TENURE-TRACK POSITION
DIRECTOR OF MEMORY DISORDERS PROGRAM
DEPARTMENT OF NEUROLOGY
GEORGETOWN UNIVERSITY MEDICAL CENTER

The Department of Neurology at Georgetown University Medical Center invites applications for a tenure-track position at the Associate or Full Professor level. The successful candidate will be Board-certified in Neurology or a related discipline, will have a track record of independently funded research in dementia, and will have strong leadership skills. This position will entail responsibility for leading the Memory Disorders Program, an active, well-established clinical research program in Alzheimer's disease and other dementias, which includes both NIH- and industry-sponsored therapeutic trials. The successful candidate will also supervise the clinical services of the Memory Disorders Program, participate in the teaching activities of the Department of Neurology and the Interdisciplinary Program in Neuroscience, and conduct his/her own research program.

Inquiries, including a current curriculum vitae and letter of interest, should be directed to:

Rhonda B. Friedman, Ph.D.
Chair, Search Committee for MDP Director
Department of Neurology, Georgetown University
207 Bldg D
4000 Reservoir Rd. NW
Washington, D.C. 20057
friedmar@georgetown.edu

Georgetown University is an Equal Opportunity/Affirmative Action Employer with a strong institutional commitment to the achievement of excellence of diversity among its faculty and staff.

CHILDREN'S HOSPITAL BOSTON
HARVARD MEDICAL SCHOOL

Neural Stem Cell/Neural Development
Assistant Professor

Applications are being considered for a tenure-track position at Children's Hospital Boston and Harvard Medical School. The successful candidate will hold either a PhD or MD degree and will join an interactive research team in the Neurobiology Program directed by Michael E. Greenberg, PhD, and Department of Neurology, Children's Hospital. This program resides within a very strong and collegial research community in neuroscience and related disciplines throughout the Harvard Medical Area. Successful candidates will have research interests in neural stem cells and/or developmental neurobiology with relevance to the pathology of the nervous system. Modern laboratory space will be available in the new Center for Life Science Building. We seek an outstanding scientist to establish a vigorous research program and form productive interactions with colleagues and other scientists at the institution. The investigators will hold both Children's Hospital Boston and Harvard Medical School faculty appointments.

Please submit a current CV, a 2- or 3-page description of research interests and directions, and three to five reference letters. Materials should be sent via email by **January 15, 2008** to:

Neural Stem Cell/Development Search
c/o Diana Phillips
diana.phillips@childrens.harvard.edu

Equal Opportunity/Affirmative Action Employer.

CAREERS IN NEUROSCIENCE

COLUMBIA UNIVERSITY
Faculty Position in Neural Engineering

The Department of Biomedical Engineering in The Fu Foundation School of Engineering and Applied Science at Columbia University invites applications for a tenure-track faculty position at the assistant, associate, or full professor level in neural engineering. Level appointment depends on qualifications. Specific areas of interest include neuroimaging, neural tissue engineering, neuromorphic engineering, computational neural modeling, and brain machine interfaces. Successful candidates must demonstrate an ability to develop a world-class research program, be capable of obtaining competitive external research funding, and participate in and be committed to outstanding teaching at both the undergraduate and graduate levels. Candidates should have a doctorate in biomedical engineering or a related discipline.

Applicants should send a complete curriculum vitae, three publication reprints, a statement of research interests, a statement of teaching experience and philosophy, and names and contact information for four references to **Professor Paul Sajda, Chair, Faculty Search Committee, 351 Engineering Terrace, MC 8904, 1210 Amsterdam Avenue, Columbia University, New York, NY 10027 by February 1, 2008. Materials can also be e-mailed to ps629@columbia.edu.**

The search will remain open until the position has been filled.

Columbia University is an affirmative action/equal opportunity employer. Women and minorities are encouraged to apply.

POSITIONS OPEN

TENURE TRACK FACULTY POSITION IN STRUCTURAL BIOLOGY
University of Maryland Biotechnology Institute – Shady Grove
Center for Advanced Research in Biotechnology
Center for Biosystems Research

As part of a major new expansion, the University of Maryland Biotechnology Institute (UMBI) invites applications for a tenure-track faculty position (Assistant Professor) in Structural Biology (X-ray crystallography or NMR spectroscopy). The successful candidate will be expected to develop a competitive and externally funded research program using structural biology approaches to address contemporary biological questions.

The Shady Grove Campus of UMBI includes scientists from the Center for Advanced Research in Biotechnology (CARB; **http://www.umbi.umd.edu/CARB**), the Center for Biosystems Research (CBR; **http://www.umbi.umd.edu/CBR**), and the National Institute of Standards and Technology (NIST). The campus is located in the heart of a major biotechnology community with easy access to the National Institutes of Health and NIST. The successful candidate will benefit from existing strengths in structural biology, biophysical chemistry, and computational biology at CARB, and from research into complex biological systems and pathobiology at CBR. State-of-the art facilities and support for X-ray crystallography and NMR are available at Shady Grove.

Qualifications: Ph.D. in Biochemistry or related field, postdoctoral experience and knowledge skills in structural biology. Applicants will be considered who have research interests in any area of contemporary structural biology, including biomedical, plant or insect biology. Applicants should submit their curriculum vitae (referencing **position #300881**), a summary of research accomplishments and future research plans, and names of three references (**PDF file**) electronically to **carbsrch@umbi.umd.edu**. Review of candidates will begin **November 8, 2007**, and continue until the position is filled.

UMBI is an EEO/ADA/AA Employer.

Chair, Department of Molecular Medicine

Located in Ithaca, N.Y., Cornell University is a bold, innovative, inclusive and dynamic teaching and research university where staff, faculty, and students alike are challenged to make an enduring contribution to the betterment of humanity.

Cornell University, College of Veterinary Medicine, invites applications and nominations for the position of Chair of the Department of Molecular Medicine. Internationally recognized faculty research programs in the department are currently focused on using molecular, cellular, and biophysical approaches to study signal transduction, cancer biology, membrane trafficking, and neurotransmitter receptor structure and function. We are seeking a scholar of recognized scientific stature and leadership ability to extend the tradition of distinction in these areas. Requirements include a Ph.D, DVM or MD and a sustained, high caliber, extramurally-funded research program.

Cornell has dramatically expanded Life Sciences research, most recently with the establishment of an Institute for Cell and Molecular Biology. This expansion has been catalyzed by Research Centers that are at the forefront of approaches to biomedical problems, including the Cornell High Energy Synchrotron Source, the Cornell Nanoscale Science and Technology Facility, and the Developmental Resource for Biophysical Imaging Opto-electronics. The new Chair of Molecular Medicine will be expected to continue to build upon these strengths in the Life Sciences by hiring outstanding new faculty and by fostering interdisciplinary interactions with these and other departments and units on the Ithaca Campus and at the Weill Cornell Medical School, including Biomedical Engineering, Chemical Biology, the Comparative Cancer Program, and the Center for Vertebrate Genomics. Relevant web links are available at: **www.vet.cornell.edu/mmedchair/**

Cornell University is situated in picturesque Ithaca, NY. This setting offers a wonderful, affordable living environment together with an academic setting that fosters a thriving tradition of collegiality and interdisciplinary work.

Applications should include a letter of nomination or intent outlining career goals, professional interests, and leadership positions, a curriculum vitae, and the names and addresses of 3 individuals who may be contacted by the Search Committee to provide references. Applications should be submitted electronically as a pdf file to: **molecularmedicinechair@cornell.edu**

Cornell University

Cornell University is an Affirmative Action/ Equal Opportunity Employer and Educator.

http://chronicle.com/jobs/profiles/2377.htm

Johns Hopkins Medical Institutions Tenure-Track Positions

Influenza and Respiratory Virus Translational Research

Human Immunology, Vaccinology, Pharmacology

The Division of Infectious Diseases of the Johns Hopkins School of Medicine is recruiting 1-2 faculty at the Assistant or Associate Professor level to contribute to an emerging institutional Respiratory Viruses Program. Our focus is on persons with proven capabilities to conduct independent research on respiratory infections, especially investigations that contribute to the prevention or treatment of influenza in humans. This recruitment contributes to expanding programs in influenza virology, structural biology, and vaccine testing. Emphasis will be given to researchers with complementary research such as in molecular biology of viral replication, host virus interactions, and quantitative analysis of viral dynamics.

Candidates must have earned an MD and/or PhD degree and have a record of acquiring research funding and producing outstanding scholarship. Salary and resources will match experience.

Candidates should provide a curriculum vitae, a one-page statement of career interest, and 3 professional references to: **Dr. David Thomas, Chief Infectious Diseases, Johns Hopkins School of Medicine, Suite 437 1830 Monument Street, Baltimore, Maryland 21205** or by email care of Nadia Hay **nhay@jhmi.edu**. Application review will begin in Fall 2007.

Johns Hopkins is an Equal Opportunity Employer.

NATIONAL RESEARCH COUNCIL

OF THE NATIONAL ACADEMIES

Research Associateship Program

Postdoctoral Research Awards
Senior Research Awards
Summer Faculty Fellowships
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offered for research at
US government laboratories

Opportunities for postdoctoral and senior research in all areas of science and engineering

- Awards for independent research at approximately 100 participating laboratory locations
- 12-month awards renewable for up to 3 years
- Annual stipend $41,000 to $70,000 - higher for senior researchers
- Relocation, professional travel, health insurance
- Annual application deadlines Feb. 1, May 1, Aug. 1, Nov. 1

Detailed program information, including instructions on how to apply, is available on the NRC Web site at :

www.national-academies.org/rap

Questions should be directed to :

National Research Council
TEL: (202) 334-2760
E-MAIL: rap@nas.edu

Qualified applicants will be reviewed without regard to race, religion, color, age, sex or national origin.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

FACULTY POSITION
Department of Chemistry
Arts and Science

The Department of Chemistry at New York University, located in Greenwich Village in lower Manhattan, invites applications for a faculty position in experimental biophysical chemistry. Strong candidates in other fields of experimental chemistry also will be considered, especially in areas of nanoscience and materials chemistry. The appointment will begin September 1, 2008, pending final administrative and budgetary approval. The search will focus on the Assistant Professor level, but exceptional candidates at higher rank can be considered. The Department is embarking on a significant growth plan that includes the creation of the Molecular Design Institute, the recent hire of two senior-level faculty with more anticipated, and expansion of laboratory and instrumentation facilities. Applicants should have a very strong research record and a commitment to teaching.

Applications should include a curriculum vita, a list of publications, a statement of future original research and teaching plans, and the names of at least three references. *Application review will begin on **November 15, 2007***. Therefore, to guarantee full consideration complete applications should be sent to **Faculty Search Committee, Department of Chemistry, New York University, 100 Washington Square East, New York, NY 10003** by this date.

NEW YORK UNIVERSITY

NYU is an Equal Opportunity/Affirmative Action Employer.

LOUISIANA STATE UNIVERSITY

Department of Environmental Studies
Baton Rouge, Louisiana 70803

ASSISTANT/ASSOCIATE/FULL PROFESSOR

(Three positions/Tenure-track)
School of the Coast and Environment

The Department of Environmental Studies within the LSU School of the Coast and Environment is building its interdisciplinary education and research program in Environmental Science, Management and Policy by hiring three tenure-track faculty. These positions will further the University's Flagship Agenda, and are designed to build on departmental strengths and provide synergy and linkages to existing programs. The Department of Environmental Studies currently offers a MS in Environmental Sciences, and is working with other units in developing a doctoral and a bachelor degree program. The Department and the School of the Coast and Environment are strongly committed to diversity and encourage applications from individuals with varied backgrounds and perspectives.

Required Qualifications: Ph.D. in environmental sciences or related field at the time of appointment; establish or have established strong programs of research and extramural funding; excel in teaching and graduate mentoring; work collaboratively to address compelling questions in environmental sciences.

We seek applicants from one or a combination of the following areas of expertise:

- **Air Quality** – air pollution, atmospheric transport modeling, health impacts and risk assessment, air sheds policy analyses.
- **Water Quality** – water pollution, water resource management, and health impact modeling. Experience in process-based modeling at watershed scale is preferred.
- **Environmental Chemistry** – chemical and physical properties of environmental chemicals, fates and effects, chemical hazards and risk assessments, trace detection of environmental pollutants.
- **Environmental Epidemiology** – environmental and public health risk assessment, uncertainty modeling, health policies and planning.
- **Environmental Economics, Planning and Management** – environmental decision making, urban planning, environmental and economic sustainability.

Additional Qualifications Desired: Expertise in geospatial technology including remote sensing and GIS and quantitative/statistical skills; ability to employ an integrated, system approach in addressing global environmental problems. An offer of employment is contingent on a satisfactory pre-employment background check. Application deadline is **December 3, 2007** or until candidates are selected. Appointments will begin in August 2008. Applicants should submit a letter describing their research and teaching interests, a current C.V. (including e-mail address) and the names and contact information (with e-mail addresses) for three referees to: **Chair, Department of Environmental Studies, 1285 Energy, Coast and Environment Building, Louisiana State University, Ref: Log #1063, Baton Rouge, LA 70803-5705. E-mail: nlam@lsu.edu.**

LSU IS AN EQUAL OPPORTUNITY/EQUAL ACCESS EMPLOYER.

London Research Institute

Research Group Leaders

CANCER RESEARCH UK
LONDON RESEARCH INSTITUTE
LINCOLN'S INN FIELDS
CLARE HALL

Cancer Research UK is the largest independent cancer research organisation in Europe, conducting wide-ranging programmes in basic, applied and clinical research. The London Research Institute (LRI) is Cancer Research UK's flagship research institute, operating on two sites, Lincoln's Inn Fields in Central London, and Clare Hall in Hertfordshire.

Research at LRI centres on the analysis of fundamental biological processes involved in cancer, with core interests in signal transduction processes and maintenance of genomic integrity. The Institute's international staff work in 50 research groups, housed in well-supported laboratories with state-of-the-art scientific support facilities.

The LRI encourages pursuit of ambitious and longer term research approaches at the highest level. We are seeking innovative scientists to establish independent research programmes at either the London LRI Lincoln's Inn Fields or Clare Hall Laboratories and to contribute to the Institute's vibrant scientific programme.

LRI scientists are funded directly through the Institute's core grant from Cancer Research UK. Support for new scientists includes a substantial laboratory space and equipment package and funding for personnel (research fellows, graduate students and technical support) and laboratory consumables. Appointments are initially for six years, with consideration for promotion to Senior Group Leader in the fifth year.

For 2008 recruitment, we are interested in scientists using biochemical and/or genomic approaches to address fundamental questions in the area of:

Chromosome biology and gene expression

including but not limited to

chromosome structure and dynamics; chromatin modifications; biochemistry of gene expression; regulatory RNAs; epigenetics

Suitably experienced applicants may be appointed at a more senior level.

Outstanding candidates working in any area of basic cancer biology which complements the interests of the Institute will also be considered favourably: our primary criterion for appointment will be the quality of the scientist.

Informal enquiries should be made by e-mail to

richard.treisman@cancer.org.uk

For information about the London Research Institute, its staff, and their research interests visit

http://www.london-research-institute.co.uk/

Applications should be submitted electronically to Dr Ava Yeo at the address below and must include:

1. Complete CV
2. Past and current research interests (approx 500 words)
3. Future research proposals (1,000-1,500 words)

THREE REFEREES should be instructed to submit letters of recommendation at the time the application is submitted

Dr Ava. Yeo, Cancer Research UK London Research Institute

Lincoln's Inn Fields Laboratories, 44 Lincoln's Inn Fields, London WC2A 3PX UK.

E-mail: Ava.Yeo@cancer.org.uk Confidential Fax (references only): (44)-20-7269-3585

APPLICATIONS SHOULD BE RECEIVED BY 17th DECEMBER 2007

Charity no: 1089464

TEXAS STATE UNIVERSITY
SAN MARCOS

The rising STAR *of Texas*

Texas State University-San Marcos is a member of the Texas State University System.

Assistant Professor
Wildlife Ecology/Conservation Biology

The Department of Biology at Texas State University–San Marcos (**www.bio.txstate.edu**) seeks a tenure-track Assistant Professor to participate in our Wildlife Ecology and Population and Conservation Biology programs. Our campus is situated within a biologically and environmentally diverse region with numerous unique and endangered native species. The successful candidate will develop a student-oriented program of field research, use quantitative approaches to address basic and/or applied questions, and complement the existing strengths of our 32-member faculty. Applicants must have an earned Ph.D. in Biology or related field and a record of research accomplishments. Preference will be given to individuals with postdoctoral training and a demonstrated ability to develop an externally funded program of research.

Review of applications will begin **January 3, 2008** and continue until the position is filled. Curriculum vitae, statements of research and teaching interests, copies of up to five representative publications, and names and addresses of three potential references should be sent as a single PDF file to **wildlife-ecology@txstate.edu**. Questions about this position should be addressed to **Dr. Dittmar Hahn, dh49@txstate.edu, Texas State University-San Marcos, 601 University Drive, San Marcos, TX 78666.**

Texas State University is an Affirmative Action/ Equal Opportunity Employer.

ASSISTANT PROFESSOR

Toxicology/ Molecular and Cellular Biology

The department of Biological Sciences at the University of Alabama invites applications for a tenure-track position at the rank of Assistant Professor in Molecular and Cellular Biology to begin August 2008. Applicants must have a Ph.D. in the Biological Sciences, postdoctoral experience, and a strong publication record. The successful candidate will be expected to develop an active extramurally funded independent research program involving, but not limited to, research in molecular toxicology. Applicants using model organisms to investigate problems in molecular toxicology, including cellular stress response mechanisms, are particularly encouraged to apply. The successful applicant will be expected to interact with and enhance existing research groups in Molecular and Cellular Biology, and will have an interest in developing quality instruction at the undergraduate and graduate levels, with course responsibilities within areas of expertise and departmental needs. The ideal candidate will demonstrate the potential to develop a multi-disciplinary research program involving collaborative interactions with faculty in the Departments of Chemistry, Chemical Engineering, and/or Metallurgical & Materials Engineering.

To apply, mail hardcopies of *curriculum vitae*, a letter of application that includes your research interests and goals, a statement of teaching philosophy, a list of courses in your area of expertise, and have three letters of reference sent to: **Search Committee - Molecular Toxicologist, Department of Biological Sciences, Box 870344, The University of Alabama, Tuscaloosa, AL 35487**. Questions about the position may be addressed to Dr. Stevan Marcus, Chair of the Search Committee (**smarcus@bama.ua.edu**, 205-348-8094). Review of applications will begin January 7, 2008, and continue until the position is filled.

For more information visit our website at **http://www.as.ua.edu/biology**

The University of Alabama is an Affirmative Action/Equal Opportunity Employer. Applications from women and minorities are encouraged.

Crimson is
THE UNIVERSITY OF ALABAMA

UMBI
SHADY GROVE

Tenure Track Faculty Position in Metabolomics
University of Maryland Biotechnology Institute – Shady Grove
Center for Advanced Research in Biotechnology
Center for Biosystems Research

Applications are invited for a tenure-track faculty position at the Assistant, Associate, or Professor level. The successful candidate will be expected to develop a rigorous, externally funded research program in the field of metabolomics using advanced analytical methods.

The Shady Grove Campus of the University of Maryland Biotechnology Institute (UMBI) is developing an integrated research program in molecular systems biology, bridging the interests of the Center for Advanced Research in Biotechnology (CARB, **http://www.umbi.umd.edu/CARB**), a partnership with the National Institute of Standards and Technology (NIST)) and the Center for Biosystems Research (CBR, **http://www.umbi.umd.edu/CBR**). Research areas at the Shady Grove Campus include chemical biology, mass spectrometry, structural biology, bioinformatics, experimental and computational biophysics, systems modeling, plant and insect biology. Several new faculty hires are anticipated over the next two years, and a new 140,000 ft^2 research building equipped with state-of-the-art facilities has recently opened.

Qualifications: Ph.D. in Biochemistry or related field, postdoctoral experience and knowledge skills in metabolomics. Areas of interest include but are not limited to: metabolite changes in response to disease or environmental stress; applications in functional genomics; metabolic networks; medicinal plant metabolism; development of metabolomic databases. We are particularly interested in applicants who are seeking a highly collaborative research environment. Applicants should submit their curriculum vitae (referencing **position #300879**), a summary of future research plans, and names of three references (**PDF file**) electronically to **carbsrch@umbi.umd.edu**. Review of candidates will begin **November 8, 2007** and continue until the position is filled.

UMBI is an EEO/ADA/AA Employer.

BERKELEY LAB

Senior Biological Engineer

JBEI
JOINT BIOENERGY INSTITUTE

Lawrence Berkeley National Laboratory (LBNL) is a world leader in science and engineering research, with 11 Nobel Prize recipients. LBNL conducts unclassified research across a wide range of scientific disciplines and hosts four national user facilities. **www.lbl.gov**

The Joint BioEnergy Institute (JBEI) led by LBNL, is a multi-organizational concentration of world-class facilities and expertise. The goal of JBEI is to use rapidly advancing scientific areas such as nanotechnology and synthetic biology to accelerate the nation's biofuel industry. **http://jbei.lbl.gov**

This senior level position will manage the day-to-day operations and research activities of the group responsible for developing feedstock, i.e., energy crops as a biofuel alternative. The incumbent must have demonstrated success in establishing and operating a viable, large-scale scientific research program, as well as supervisory experience with various levels of research support staff, and interpersonal skills necessary to effectively lead a multi-site research team. The candidate must also have a published record of high impact work as evidenced by publications in internationally recognized and peer-reviewed journals. Extensive experience in molecular biology, transgenic plants, and characterization of complex carbohydrates and their synthesis is also essential.

Please apply online at: **http://jobs.lbl.gov**, select "Search Jobs", and enter 20959 in the keyword search field. Submit a single attachment including your resume/CV and letter of interest. Reference "Newspaper/Journal" and "Science" as your source. AA/EOE

POSTDOCTORAL FELLOW

MARSHFIELD CLINIC.

We invite applications for a postdoctoral fellow position in the Molecular Microbiology Laboratory (PI: Dr. Sanjay K. Shukla) of Marshfield Clinic Research Foundation. The selected candidate is expected to work on new and ongoing research studies focusing on evolution of virulence in methicillin-resistant Staphylococcus aureus.

For recent publications visit: http://www.marshfieldclinic.org/crc/pages/default.aspx?page=InvestigatorDirectory&id=244&pubs=true#publications.

Research experience in bacterial virulence mechanisms, bioinformatics, or molecular epidemiology preferred. A Ph.D. in microbiology or molecular biology or related disciplines is required. 1-2 years of postdoctoral experience would be advantageous. Salary and benefits will be commensurate with Marshfield Clinic guidelines.

Interested individuals should send a cover letter, curriculum vitae, and contact information for three references to:

Marshfield Clinic - Attn: HR
1000 North Oak Avenue
Marshfield, WI 54449
Phone: 715.389.3288

Marshfield Clinic is an Affirmative Action/ Equal Opportunity Employer that values diversity. Minorities, females, individuals with disabilities and veterans are encouraged to apply.

CSIC

265 POSTDOCTORAL CONTRACTS AT CSIC

The Spanish National Research Council (CSIC) offers 265 new postdoctoral contracts distributed among its 116 research institutes throughout Spain. This offer is opened to researchers with a doctorate degree obtained within the last ten years. Contracts will have three years duration to work within priority research groups and lines as defined in the CSIC's Action Plan for 2006-2009, and the respective Strategic Plans of centres and institutes. Contract profiles encompass a wide range of research areas that goes from life and material sciences to human and social sciences.

Deadline for applications: November 9th 2007.

General requirements as well as details on the selection process can be found at **www.csic.es**. This offer is part of the CSIC "Junta para la Ampliación de Estudios" (JAE) Programme to train researchers and technicians.

London Research Institute

CANCER RESEARCH UK
LONDON RESEARCH INSTITUTE
LINCOLN'S INN FIELDS
CLARE HALL

Research Group Leaders

Cancer Research UK is the largest independent cancer research organisation in Europe, conducting wide-ranging programmes in basic, applied and clinical research. The London Research Institute (LRI) is Cancer Research UK's flagship research institute, operating on two sites, Lincoln's Inn Fields in Central London, and Clare Hall in Hertfordshire. Research at LRI centres on the analysis of fundamental biological processes involved in cancer, with core interests in signal transduction processes and maintenance of genomic integrity. The Institute's international staff work in 50 research groups, housed in well-supported laboratories with state-of-the-art scientific support facilities.

The LRI encourages pursuit of ambitious and longer term research approaches at the highest level.

We are seeking innovative scientists to establish independent research programmes at the London Research Institute's Lincoln's Inn Fields Laboratories and to contribute to the Institute's vibrant scientific programme. The London Research Institute is core funded by Cancer Research UK and group leaders at the Institute are provided with laboratory space and core personnel (including technical support, research fellows and graduate students) together with generous funding for laboratory equipment and consumables, as well as cost-free access to scientific support facilities (including biological resources, transgenic facilities, flow cytometry, confocal microscopy, DNA sequencing, peptide synthesis, etc).

For 2008 recruitment, we are interested in scientists using molecular and cellular approaches to address questions in the area of:

Immunology

including

T cell tolerance and immunity;
NK cell biology; inflammation and innate immunity

Appointments will be made at junior or senior level according to experience.

(Junior appointments are for six years in the first instance with consideration for promotion to Senior Group leader in the fifth year)

Informal e-mail enquiries may be made to Caetano Reis e Sousa at: caetano@cancer.org.uk

For information about the London Research Institute, its staff, and their research interests visit http://www.london-research-institute.co.uk/

Applications should be submitted electronically to Dr Ava Yeo at the address below and must include:

1. **Complete CV**
2. **Past and current research interests (approx 500 words)**
3. **Detailed outline of future research proposals (approx 1000 words)**
4. **Contact details of three academic referees**

Dr Ava Yeo, Cancer Research UK London Research Institute

Lincoln's Inn Fields Laboratories, 44 Lincoln's Inn Fields, London WC2A 3PX, UK.

E-mail: Ava.Yeo@cancer.org.uk;

Confidential Fax (references only): (44)-20-7269-3585

APPLICATIONS SHOULD BE RECEIVED BY 17th DECEMBER 2007

Charity no: 1089464

Tenure-track Position in Computational Biology and Bioinformatics

Located in Ithaca, N.Y., Cornell University is a bold, innovative, inclusive and dynamic teaching and research university where staff, faculty, and students alike are challenged to make an enduring contribution to the betterment of humanity.

Applications are invited for a tenure-track position in Computational Biology in the Computer Science department of Cornell University. Multiple positions are available, and depending on experience positions can be at the assistant, associate, or full professor level. Applicants must possess a Ph.D. in computer science or Ph.D. in mathematical, biological or physical science with enough expertise in computer science to fit within a CS department. The department requires demonstrated research abilities at the highest level as well as outstanding teaching ability and leadership qualities.

Outstanding applicants in all areas of computational biology will be considered. We are especially interested in areas including regulatory networks, population genetics, and complex behavior at the sub-cellular and cellular levels.

To ensure full consideration, applications should be received by December 1, 2007, but will be accepted until all positions are filled.

Applicants should submit a curriculum vita, brief statements of research and teaching interests through the web at **http://www.cis.cornell.edu/apply**, and arrange to have at least three references uploaded on the Web or sent to: **Stacey Shirk, Department of Computer Science, 4130 Upson Hall, Cornell University, Ithaca, NY 14853-7501** or **frecruit@cs.cornell.edu**

Cornell University

Cornell University is an Equal Opportunity Employer and encourages applications from women and ethnic minorities.

http://chronicle.com/jobs/profiles/2377.htm

UNIVERSITY of IOWA CARVER COLLEGE OF MEDICINE

Assistant Professor
Department of Anatomy and Cell Biology

The University of Iowa, Department of Anatomy and Cell Biology, **http://www.anatomy.uiowa.edu/**, invites applications for tenure-track faculty positions in Molecular Medicine at the rank of Assistant Professor. This is a 12-month appointment with a highly competitive start-up package, laboratory space, salary and benefits. Outstanding candidates interested in the pathophysiology of human disease and animal models are encouraged to apply.

Current strengths in the department include cell and developmental biology, cardiovascular biology, neurobiology, cancer, and stem cell biology. The Department of Anatomy and Cell Biology is also the administrative home of the Center for Gene Therapy. **http://genetherapy.genetics.uiowa.edu/**

Candidates must hold a Ph.D., M.D., or equivalent degree, with at least two years of relevant postdoctoral research experience. The successful applicant will have a strong record of research productivity and publications in excellent peer-reviewed high-impact scientific journals, and exhibit a high potential to develop a successful extramurally funded research program. In addition, the applicant will have demonstrated experience working effectively in a diverse research environment.

Applicants should submit a curriculum vitae, a short statement of research interests and plans, and the names of at least three references to the address below. Review of applicants will begin immediately. Please send all materials to:

Molecular Medicine Search Committee
Department of Anatomy and Cell Biology
1-100A BSB
The University of Iowa
51 Newton Road
Iowa City, IA 52242

The University of Iowa is an Equal Opportunity and Affirmative Action Employer. Women and minorities are strongly encouraged to apply.

MICHIGAN STATE UNIVERSITY

PLANT FUNCTIONAL ECOLOGIST

The Department of Plant Biology at Michigan State University invites applications for a tenure-track position at the **Assistant Professor** level. We seek an individual who investigates the ecological significance of **physiological**, **morphological**, and/or **developmental** traits. We are particularly interested in applicants who employ phylogenetic and/or molecular genetic methods. This position complements a number of recent hires in ecology, evolution, population genetics, developmental biology, and bioinformatics at MSU. The successful applicant will contribute to undergraduate and graduate teaching, participate in the graduate program in Ecology, Evolutionary Biology, and Behavior (**www.msu.edu/~eebb**), and maintain an externally funded research program. Applicants must have a Ph.D., and postdoctoral research experience is desirable.

Applications should include a curriculum vitae, a summary of research accomplishments and future research objectives, a brief description of teaching philosophy and goals, and three letters of reference. Information about the Department of Plant Biology can be found at **http://www.plantbiology.msu.edu**. The review of applications will begin **November 30, 2007** and will continue until a suitable candidate is identified. Application materials should be sent electronically to **plbeco@msu.edu**. Questions regarding this position may be sent to **Douglas Schemske (schem@msu.edu)**.

MSU is an Affirmative Action, Equal Opportunity Employer. MSU is committed to achieving excellence through cultural diversity. The university actively encourages applications and/or nominations of women, persons of color, veterans and persons with disabilities.

OPEN EXAMINATIONS FOR:
ASSOCIATE TOXICOLOGIST
STAFF TOXICOLOGIST

The Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency announces recruitment for the **Associate and Staff Toxicologist examinations** for the purpose of establishing hiring lists. Openings exist in Sacramento, California. Persons experienced in conducting human health pesticide exposure assessments or evaluating toxicological or exposure studies are encouraged to apply. To qualify for the Associate Toxicologist, an entry level position, persons must: (1) hold a doctoral degree in Toxicology, Biochemistry, Pharmacology or a closely related field; or (2) hold a master's degree in toxicology or a closely related field **and** three years post-master's experience in designing and managing toxicological studies, interpreting results, and conducting hazard assessment or safety evaluations; or (3) have certification as a Diplomat of the American Board of Toxicology. To qualify for Staff Toxicologist, persons must hold a doctoral degree in Toxicology, Biochemistry, Pharmacology or a closely related field **and** a minimum of 3 years of post-doctoral experience, in the interpretation of toxicological findings relative to probable human health or aquatic life hazards and one year of experience in the development and design of toxicological research and investigative studies. The required degrees for these examinations must have been obtained from an accredited college or university. Candidates must meet the qualifications as stated in the official examination bulletin by the cutoff date indicated below. The salary ranges for Associate and Staff Toxicologist are **$4,833 - $6,404** and **$6,409 - $7,753 per month**, respectively.

If interested, please submit your resume and a copy of the Examination Application (STD 678), available at: **http://www.spb.ca.gov/Employment/employment_forms_brochures.htm**, to the following: **Department of Pesticide Regulation, Personnel Services Branch/Examinations Unit, 1001 "I" Street, 4th Floor, P.O. Box 4015, Sacramento, California 95812-4015**.

The testing office will accept applications postmarked no later than **November 19, 2007** for the initial testing period. Applications received after this date will be held until the next round of testing. Refer to the official bulletin for specific requirements and examination information at **http://www.cdpr.ca.gov/docs/dept/psb/home.htm**. Contact the **DPR Examination Unit** at **(916) 322-4553** for any questions.

University of Wyoming

ATMOSPHERIC SCIENCE AND RENEWABLE RESOURCES
Wyoming Excellence Chair in Ecological Climatology

The Departments of Atmospheric Science and Renewable Resources at the University of Wyoming seek a distinguished scholar for the new Wyoming Excellence Chair in Ecological Climatology. This endowed position will be filled at the rank of associate or full professor. It is expected that the successful candidate will have an earned Ph.D. degree in atmospheric science, ecology or in a closely related field, and should be eligible for appointment with tenure in the Department of Atmospheric Science. Candidates with an internationally recognized research program focused on processes controlling the land-atmosphere exchange of water, trace gases, aerosols, and/or energy are invited to apply. Preference will be given to those involved with measurements and their incorporation into climate models linking the atmosphere to terrestrial ecosystems. The successful candidate will be expected to maintain an active research program, advise graduate students, manage a research team, and develop courses such as climate-ecology interaction or climate change dynamics. The position includes a very attractive start-up package and access to a suite of research facilities, including an NSF-supported King Air research aircraft (**http://flights.uwyo.edu/**), the Stable Isotope Facility (**http://uwacadweb.uwyo.edu/sif/**), the Environmental Simulation Laboratory, the W. M. Keck Aerosol Laboratory, and the Elk Mountain Observatory.

In addition to the mostly observational research programs in atmospheric science and renewable resources, the University has a strong cross-disciplinary doctoral Program in Ecology (PiE, **http://uwacadweb.uwyo.edu/PIE/**) and is forging new ties with the National Center for Atmospheric Research (NCAR) through joint supercomputing endeavors. The successful candidate is expected to interact with faculty and students in PiE, and with NCAR scientists.

Applications must include (a) a letter of interest, (b) a statement of research intentions, tools, and linkages, (c) a brief statement about teaching interests, (d) a list of the five most relevant publications, all publicly accessible, (e) the names and contact information for at least three references, and (f) a curriculum vitae. Screening of applications will begin **December 3, 2007** and continue until the position is filled.

Applications may be mailed to:

Ecoclim Search Committee
Dept. of Atmospheric Science, Dept. 3038
1000 E. University Avenue
Laramie, WY 82071, USA

Email submissions are preferred: **ecoclim@uwyo.edu**

For additional information, please contact the search committee chair, **Bart Geerts Laramie, WY 82071, USA (geerts@uwyo.edu, +1-307-766-2261)**

The University of Wyoming is a Carnegie Foundation Research/Doctoral Extensive Institution, and adheres to the principles of equal employment opportunity and diversity and welcomes applications from qualified individuals, independent of race, color, religion, sex, national origin, disability, age, veteran status, sexual orientation or political belief. We welcome applications from diverse groups, including women and people of color, and international candidates.

Cornell University

Institute for Cell and Molecular Biology
Senior and Junior Faculty Positions

Second Call for Applications

As part of a New Life Science Initiative, Cornell University has established and endowed a new Institute for Cell and Molecular Biology (for complete information, see **www.icmb.cornell.edu**). The Institute will consist of 12 faculty as the core component in a $160M new research building, now nearing completion, designed by renowned architect Richard Meier. Dr. Scott Emr recently relocated to Cornell as the founding Director of the new Institute. The goal of the Institute is to build a vibrant center of scientific excellence in basic biology integrated with existing outstanding programs in chemistry and chemical biology, physics, computational biology and engineering. Institute faculty will have full academic appointments in basic science departments to which they will contribute teaching and service.

Three faculty positions are available this year, one of which will be an Endowed Professorship (department open) and the others appointed at the Assistant or Associate Professor levels within the department of Molecular Biology & Genetics (**www.mbg.cornell.edu**). Priority will be given to candidates using model systems employing novel approaches to address fundamental questions in cell biology (including cell cycle control, signal transduction, regulation of the cytoskeleton, organelle biogenesis and function, regulation of membrane architecture, protein quality control, etc.). Individuals with expertise in X-ray crystallography, biochemical reconstitution, mass spectrometry, functional genomics, and live cell imaging are of special interest. However, outstanding candidates in any area of cell and molecular biology will be considered.

Please submit (electronically) a curriculum vitae (highlighting 3-5 publications with title and abstract), research plan (2-3 pages) and teaching interests. Please limit total file to 10MB. In addition, applicants must arrange for three letters of recommendation to be sent to the e-mail address below, concurrent with the other application materials. The committee will evaluate completed applications received before December 15, 2007, with later applications being considered until the positions are filled. We encourage women and minorities to apply.

Applications must be submitted electronically, as a single pdf, to:
Dr. Scott Emr, c/o Dianna Marsh at
dmm20@cornell.edu

Cornell University is an Affirmative Action/ Equal Opportunity Employer and Educator.

MONTEREY BAY AQUARIUM RESEARCH INSTITUTE

POSTDOCTORAL FELLOWSHIPS IN THE OCEAN SCIENCES

Founded in 1987 and supported by the David and Lucile Packard Foundation, The Monterey Bay Aquarium Research Institute (MBARI) is a non-profit oceanographic research institute, dedicated to the development of state-of-the-art instrumentation, systems, and methods for scientific research in the oceans. MBARI's research center includes science and engineering laboratories, as well as an operations facility to support our research vessels and oceanographic equipment, including remotely operated and autonomous underwater vehicles. Located in Moss Landing, California, the heart of the nation's largest marine sanctuary, MBARI places a balanced emphasis on science and engineering, with established programs in marine robotics, ocean physics, chemistry, geology, and biology, as well as information management and ocean instrumentation research and development.

MBARI invites applications each year for several postdoctoral fellowships in the fields of biological, chemical, and physical oceanography, marine geology, and ocean engineering. Fellowships may require occasional trips to sea. Awards are typically for two years.

Candidates must awarded their Ph.D. degree prior to commencing the two-year appointment between September 2008 and March 2009.

Application deadline: Thursday, December 13, 2007

Selected candidates will be contacted in March 2008.

Note: Applicants are encouraged to communicate with potential research sponsors at MBARI **(http://www.mbari.org/about/researchers.html)** for guidance on project feasibility, relevance to ongoing MBARI research, and resource availability.

Application requirements:
1. Curriculum vitae
2. At least three professional letters of recommendation
3. Succinct statement of the applicant's doctoral research
4. Potential research goals at MBARI
5. Supplemental Information online form **(http://www.mbari.org/oed/jobs/forms/postdoc_form.htm)**

Competitive compensation and benefits package.
MBARI considers all applicants for employment without regard to race, color, religion, sex, national origin, disability, or veteran status.

Address your application materials to:
MBARI, Human Resources
Job code: Postdocs-2008
7700 Sandholdt Road, Moss Landing, CA 95039-9644

Submit by e-mail to **jobs_postdocs@mbari.org** (preferred), by mail, or fax to (831) 775-1620.

M B A R I

EOE • MBARI Welcomes Diversity

Beijing Institute of Genomics (BIG), Chinese Academy of Sciences

Full Professors, Associate Professors and 100 talents program professors
Director or Deputy-Director of Administrative Departments

Beijing Institute of Genomics (BIG) is one of the youngest institutions of Chinese Academy of Sciences, founded on the basis of Beijing Genomics Institute (BGI) and made significant contribution to the International Human Genome Project, International HapMap Project, International Chicken Genome Sequencing and Polymorphism Projects, as well as sequencing and analysis of the rice, silkworm and other important genomes.

At the moment of moving to the temporary campus close to the central site of the 2008 Olympic Games, BIG will open to the whole society its positions of 30 Full Professors/ Associate Professors, and of 8 Directors or Deputy-Directors of Administrative Departments. Willing to work in the planned section in Suzhou are encouraged. Details can be found at **http://www.big.ac.cn.**

Deadline of application: Review of the applications will begin November 8, 2007, and will continue until positions are filled. Contact: **gongkaizhaopin@big.ac.cn**

Huanming Yang, Ph.D.
Director-General, BIG, CAS

NANYANG TECHNOLOGICAL UNIVERSITY

Faculty Appointments

School of Biological Sciences

The School of Biological Sciences at Nanyang Technological University (NTU), Singapore is seeking faculty members of various ranks. Applicants who possess a PhD, preferably with a proven track record in research and teaching at university level, are invited to apply for suitable appointments in the following areas:

- **Chemical Biology**
- **Medicinal Chemistry**
- **Natural Products and Practices in Chinese Medicine**
- **Pharmacology**

Successful applicants are expected to conduct undergraduate/postgraduate teaching and undertake research. They are also expected to participate in academic/professional activities that enrich the global development of NTU.

Suitably qualified candidates are invited to submit a completed application. Please refer to **www.ntu.edu.sg/hr/faculty_guidelines.htm**. The post applied for should be clearly stated.

Electronic submission of application is encouraged and can be forwarded to **sbsrecruit@ntu.edu.sg**. Application can also be mailed to:

Chair
School of Biological Sciences
Nanyang Technological University
60 Nanyang Drive, Singapore 637551

Details of the School can be found on **www.ntu.edu.sg/sbs**

www.ntu.edu.sg

UMDNJ
ROBERT WOOD JOHNSON MEDICAL SCHOOL
University of Medicine & Dentistry of New Jersey

The Cancer Institute of New Jersey℠

DIRECTOR, CANCER INSTITUTE OF NEW JERSEY

UMDNJ-Robert Wood Johnson Medical School seeks applications and nominations for the position of Director, Cancer Institute of New Jersey (CINJ). This is an outstanding opportunity for a physician-scientist or scientist to lead the State's first and only National Cancer Institute-designated Comprehensive Cancer Center. Candidates should be internationally recognized for their outstanding work in cancer research and dedicated to applying this new knowledge to the benefit of patients. Experience in leadership roles that will help advance the Institute in the areas of patient care, teaching, research and community outreach is essential. A skilled and energetic leader is sought who has the ability to recruit outstanding researchers, attract national cancer research grants, and who can work with community and patient advocacy groups.

Established in 1991, The Cancer Institute of New Jersey is one of the Nation's most rapidly growing cancer centers. CINJ is a matrix cancer center with 155 full members from Robert Wood Johnson Medical School and Rutgers University. Members of the Institute received approximately $100 million in research grants this past year. Patient visits have reached more than 75,000 per year and accrual to clinical trials has increased to over 1,200.

CINJ delivers advanced comprehensive care, conducts world-class cancer research, transforms laboratory discoveries into clinical practice, and provides education regarding cancer prevention, detection and treatment. CINJ also offers the latest clinical trials and experimental therapies. With a statewide reach, CINJ includes a network of 17 hospitals, making it one of the largest networks in the nation. Specialized centers include: the Dean and Betty Gallo Prostate Cancer Center, the LIFE Center for Breast Cancer Awareness, the Fannie E. Rippel Foundation Center for Women's Reproductive Cancers, and the Center for the Study of Diet and Nutrition.

As one of the eight schools of the University of Medicine and Dentistry of New Jersey with 2,500 full-time and volunteer faculty, Robert Wood Johnson Medical School encompasses 22 basic science and clinical departments and hosts centers and institutes including The Cancer Institute of New Jersey, the Child Health Institute of New Jersey, the Center for Advanced Biotechnology and Medicine, the Environmental and Occupational Health Sciences Institute, and the Stem Cell Institute of New Jersey. The medical school maintains educational programs at the undergraduate, graduate and postgraduate levels for more than 1,500 students on its campuses in New Brunswick, Piscataway, and Camden, and provides continuing education courses for health care professionals and community education programs.

Review of applications will begin immediately and continue until the position is filled. Please send nominations and/or application, including a brief statement of the attributes and quality of the individual, and curriculum vitae to: **Bonnie Baloga-Altieri, MSN, RN, CNAA, Office of the Dean, UMDNJ-Robert Wood Johnson Medical School, 125 Paterson Street, Suite 1400, New Brunswick, New Jersey 08903 OR Email: balogabl@umdnj.edu.** UMDNJ is an Affirmative Action/Equal Opportunity Employer. For more information, visit **www.umdnj.edu/hrweb**

LEHMAN COLLEGE

The **Department of Biological Sciences** at **Lehman College of The City University of New York** seeks to fill a tenure track position at the Assistant/ Associate Professor level in the area of Plant Physiology with a specialization in physiological ecology. The successful candidate should have a research interest in the effects of global climate change on temperate forest habitats. He/She will be expected to develop an active research program with extramural funding. Candidates must have a Ph.D. degree in the biological sciences, demonstrated ability to publish in peer reviewed journals, and evidence of effectiveness in teaching.

To apply, submit a letter of application, curriculum vitae, and three current letters of recommendation as both hard and electronic copies (PDF on CDROM). You may also include a statement of research interest and a PDF of no more than two of your recent peer reviewed publications. All material should be sent to: **Professor Joseph W. Rachlin, Chair, Department of Biological Sciences, Lehman College of CUNY, 250 Bedford Park Boulevard West, Bronx, New York 10468-1589**. Visit the Lehman College website: **www.lehman.edu** for the full position announcement.

Lehman College is an EEO/AA/ADA Employer.

Investigator
Statistical Genetics/Genetic Epidemiology

The Division of Statistical Genomics and the Department of Genetics at Washington University School of Medicine invite applications for an investigator (tenure)-track position in statistical genetics / genetic epidemiology. Strong background in quantitative sciences is essential, with specific expertise in statistical genetics, genetic epidemiology, or population genetics.

Experience in genomics and post-doctoral training will be advantageous. We seek individuals with a focus on theoretical and applied statistical modeling to interact with clinical and translational scientists engaged in human biomedical research from other disciplines such as oncology, cardiology, pharmacology, and microbiology. The successful candidate must be an innovative thinker capable of developing an independent research program, will participate in teaching and mentoring of graduate students, and should possess a collaborative and collegial spirit. An excellent start-up package is available, along with generous benefits.

Applications received before **January 1, 2008** will receive full consideration. To apply, please send your CV, a statement of research interests, and three references, preferably in electronic format, to: **Ingrid Borecki, Ph.D., Co-Director, Division of Statistical Genomics, Washington University School of Medicine, 4444 Forest Park Blvd. – Box 8506, St. Louis, MO 63108; dsg-faculty@dsgmail.wustl.edu**.

We strongly encourage women and underrepresented minorities to apply. Washington University is an Equal Opportunity/Affirmative Action Employer.

Washington University in St. Louis
SCHOOL OF MEDICINE

DSG
Division of Statistical Genomics

The Medical College of Georgia

The Department of Pathology at the Medical College of Georgia continues the expansion of its program in investigative pathology. We invite applications for a tenure-track faculty position at the level of Professor engaged in basic and/or translational research related to cancer. Candidates must have externally funded research programs related to the genesis, progression and prevention of cancer.

Areas of special interest include, but are not limited to, animal models of cancer, tumor-host microenvironment, and molecular control of cell proliferation and metastasis. Selected applicant will join a group of scientists investigating the role of G protein-coupled receptors and their effectors using animal models of human disease. The position is supported by a generous start-up package, and laboratories will be available in the new Cancer Center.

Applicants should have MD and /or PhD degrees and significant postdoctoral experience.

Please send curriculum vitae including a statement of research interests and future plans, and the names of three references to: **Dr Yehia Daaka, Professor and Endowed Chair, Department of Pathology, c/o Mrs. Carol Hardy, Medical College of Georgia BF104, 1120 15th Street, Augusta, Georgia 30912** or **chardy@mcg.edu**.

The Medical College of Georgia is a Minority/Female/Veterans Equal Employment Opportunity, Affirmative Action, and Americans with Disabilities Act Employer.

Faculty Position Structural Biology Program Sloan-Kettering Institute

Memorial Sloan-Kettering Cancer Center invites applications for a tenure-track faculty position at the Assistant Member level in the Structural Biology Program of the Sloan-Kettering Institute (www.ski.edu). We are interested in individuals with an outstanding record of research achievements in any area of structural biology, including x-ray crystallography, NMR spectroscopy, EM and optical imaging, as well as the interface of structural, chemical and computational biology. Faculty will be eligible to hold appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program.

Interested individuals should submit their Curriculum Vitae, description of past research accomplishments and proposed research, selected reprints and three letters of recommendation in PDF format to **strucbio@mskcc.org.** Application materials and signed letters of recommendation can also be submitted by mail to: **Dr. Nikola Pavletich, c/o Julie Kwan, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 494, New York, New York 10065.** The application deadline is **January 15, 2008.** Memorial Sloan-Kettering Cancer Center is an Equal Opportunity Employer. Smoke-free environment.

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.
www.mskcc.org

TENURE-TRACK FACULTY POSITION DEPARTMENT OF BIOCHEMISTRY

MEDICAL COLLEGE OF WISCONSIN

The Department of Biochemistry invites applications for faculty positions at the Assistant or Associate Professor level with a focus on **molecular biological** approaches employed in studying **cancer** mechanisms. Applicants must have a doctoral degree (Ph.D., M.D., or both), at least 2 years of postdoctoral training, a strong publication record, and potential to obtain extramural funding.

The Medical College of Wisconsin (**http://www.mcw.edu**) is the largest private research institution in Wisconsin, conducting over $130 million annually in funded research. Over the past several years the College has been among the fastest growing medical schools in the United States in terms of NIH funding. In addition to a strong core of basic biomedical science departments, the Medical College is home to nine federally designated Centers of Biomedical Research. Excellent shared facilities are available for proteomics, imaging, molecular biology, mouse/rat genetics, flow cytometry, mass spectrometry, electron microscopy, X-ray crystallography and nuclear magnetic resonance. The research and clinical programs benefit directly from strong philanthropic support from cancer survivors, family members, and patient advocates. The College is completing major new cancer care facilities, including a Cancer Pavilion, and has recently opened a Basic Research Building housing interdisciplinary research programs. The Medical College is conveniently located in suburban Milwaukee and is part of an academic medical center that includes nationally distinguished children's and adult hospitals that employ over 13,000 people. The College is located 8 miles west of Lake Michigan with easy access to surrounding communities, lakes, and parks.

Salary and other considerations will be competitive and consistent with the College's commitment to recruiting the best-qualified individuals. Applications should include a cover letter, curriculum vitae, statement of research interests, and 3 reference letters. The review process will begin on **November 1, 2007**. For full consideration, applications should be received by **November 30, 2007**. Send application materials and reference letters, preferably by e-mail with pdf attachments, to **cricker@mcw.edu** or by regular mail to: **Dr. Robert Deschenes, Chair, Department of Biochemistry, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.**

EOE M/F/D/V
www.mcw.edu/hr

Assistant/Associate Professor Department of Pharmaceutical Sciences North Dakota State University

The Department of Pharmaceutical Sciences at North Dakota State University invites applications for a tenure-track Assistant/Associate Professor position. Preference will be given to candidates who have expertise in the field of Pharmacogenomics. The successful candidate is expected to develop an extramurally funded research program on emerging aspects of pharmacogenomics that complements existing interests in the department, teach Pharm.D.- and graduate-level courses, mentor Pharm.D./Ph.D. students, and provide service to the University and to the discipline. Excellent communication skills and the ability to function in a team environment are essential qualities for this position. Applicants must have a doctoral degree in Pharmacogenomics, or related field, and at least two years post-doctoral experience with evidence of scholastic aptitude.

The department has experienced rapid recent growth and consists of ten full-time faculty members and 30 doctoral students. The department faculty members have diverse but complementary research interests and are well funded from numerous national and other funding agencies. The department also participates in a $10.5 million NIH-funded Center of Biomedical Research Excellence and $16.3 million NIH-funded IDeA Networks of Biomedical Research Excellence programs. Additional information pertaining to the department, the university, and Fargo can be obtained at **http://www.ndsu.edu/pharmsci/**.

The review of applications will begin on **February 1, 2008** and continue until the position is filled. The appointment is expected to begin on or after August 15, 2008. Rank and a highly competitive salary with excellent start-up package are commensurate with qualifications and experience. Interested candidates should submit a (1) letter of application, (2) statement of teaching philosophy, (3) description of research interests and future plans, (4) curriculum vitae, and (5) contact information for three professional references to **Dr. Satadal Chatterjee, Department of Pharmaceutical Sciences, College of Pharmacy, Nursing and Allied Sciences, Sudro Hall, North Dakota State University, Fargo, ND 58105, Tel: 701-231-5286, Fax: 701-231-8333, e-mail: Satadal.Chatterjee@ndsu.edu**.

NDSU is an Equal Opportunity/Affirmative Action Employer.

DTU

ONE OR MORE FULL PROFESSORSHIPS

IN THE DEPARTMENT OF CHEMISTRY

The positions are intended for candidates with strong experimental profiles and outstanding track records. At least one of the professorships will be within organic chemistry. Otherwise, priority in the selection process will be given to scientific excellence rather than to any particular field of research within experimental chemistry.

Further information can be obtained from Head of Department, Professor Ole W. Sørensen, tel.: +45 45 25 24 06; email: ows@kemi.dtu.dk.

The full text of the announcement can be seen on DTU's homepage.

Application deadline: January 4th, 2008 at 12.00.

The Technical University of Denmark is one of the largest technical research and educational institutions in Northern Europe with 7,000 students, 4,500 employees and a yearly turnover of DKK 3.1 billion. As of January 1, 2007, DTU has merged with the Danish Institute for Food and Veterinary Research, Risø National Laboratory, the Danish Institute for Fisheries Research, the Danish National Space Centre and the Danish Transport Research Institute.

Further details www.dtu.dk/vacancy

Assistant Professor or Untenured Associate Professor Department of Orthopaedic Surgery and Department of Bioengineering at Stanford University

The Department of Orthopaedic Surgery in conjunction with the Department of Bioengineering at Stanford University seeks applicants for a faculty position at the junior level (Assistant Professor or untenured Associate Professor) on the university tenure line. Applicants are expected to have a doctoral degree in bioengineering, biomedical engineering, molecular biology or a related discipline.

The candidate is expected to develop an outstanding research program in tissue engineering, regenerative medicine, biomaterials, cell or molecular engineering, or musculoskeletal bioengineering. This is intended to be a broad based search and may encompass individuals with a wide range of expertise. The candidate should have the capacity to apply biomechanics and biomaterial science to tissue engineering and orthopaedic science, and is expected to collaborate with both clinical and basic scientists to enhance ongoing interdisciplinary programs. The successful candidate will be responsible for securing government and industry funding to support and conduct innovative research.

The overriding requirement for faculty appointment, reappointment and promotion within the UTL must be distinguished performance, or (in the case of junior faculty) the promise of distinguished performance. There should be a major commitment to research and teaching. There must be outstanding accomplishments in research and excellent overall performance in teaching, as well as in clinical care and institutional service appropriate to the programmatic need the individual is expected to fulfill.

The application should comprise a brief research plan, a resume, and the names and addresses of at least five references, which should be sent to: **William J. Maloney, MD, Professor and Chair, Department of Orthopaedic Surgery, 300 Pasteur Drive, Edwards R109, Stanford, CA 94305-5335.**

Stanford University is an Equal Opportunity Employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applications from women and members of minority groups, as well as others who would bring additional dimensions to the university's research, teaching and clinical missions.

Lead the next generation of pharmaceutical science.

Discover the Answers that Matter.

Eli Lilly and Company is a leading, innovation-driven pharmaceutical corporation with approximately 42,000 employees worldwide. Lilly is developing a growing portfolio of best-in-class, first-in-class pharmaceutical products. We achieve this by applying the latest research from our own worldwide laboratories, by collaborating with eminent scientific organisations and by making use of the most up-to-date technological tools.

Established in 2002, the Lilly-Singapore Centre for Drug Discovery (LSCDD) is now expanding its capability to discover and develop new medicines more productively, in the areas of cancer and metabolic disorders. We form a network of drug development partners, and through innovative data integration approaches, discover and apply biomarker and patient-tailoring solutions.

Located in the exciting Singapore Biopolis, LSCDD's multi-disciplinary and multi-cultural team is working to redefine the leading edge. We are looking for outstanding individuals to fill the following positions:

- **Director – Drug Discovery Research**
- **Director – Integrative Computational Sciences**
- **Senior Scientist – Assay Development**
- **Senior Scientist – Cancer Biology**
- **Senior Scientist – Diabetes**
- **Senior Scientist – Epigenetics**
- **Informatics Scientist**
- **Research Associate**
- **Software Engineer**
- **BioSafety Officer**

Log on to www.lscdd.lilly.com.sg to find out more about these positions and what a career at Eli Lilly and Company can offer you. Eli Lilly is an equal opportunity employer.

www.lscdd.lilly.com.sg

Lilly
Answers That Matter.

FACULTY POSITION IN BIOLOGICAL CIRCUITS

Caltech invites applications for a tenure-track position in the broadly construed area of engineering biological circuits.

We are interested in areas such as synthetic and systems biology, circuit design and analysis, biomolecular information processing and bionanotechnology. Candidates pursuing wet, dry, *in vivo*, *in vitro*, analytic, synthetic, experimental, and/or theoretical research will be considered. A strong commitment to excellence in teaching and mentoring is also expected. The successful candidate will have a primary home in Bioengineering, Applied Physics, Computation and Neural Systems, Computer Science, Control and Dynamical Systems, Electrical Engineering, or Applied and Computational Mathematics, as well as the possibility of a joint appointment in Biology, Chemical Engineering, Chemistry, or Physics. Participation in the Center for Biological Circuit Design, part of Caltech's Information Science and Technology initiative, will provide access to an active research community with opportunities for interdisciplinary collaborations. Strong preference will be given to applicants at the assistant professor level, but exceptional candidates at the associate or full professor levels will be considered. The term of the initial appointment at the assistant professor level is normally four years, and is contingent upon completion of a PhD.

Applicants should apply online at http://www.eas.caltech.edu/bio-circuits by submitting a letter of application; a brief statement of research accomplishments, interests, and goals; a brief statement of teaching interests; curriculum vitae; and up to three selected reprints or preprints. Applicants should arrange to have four letters of reference uploaded to http://www.eas.caltech.edu/bio-circuits/refs/. Application review will commence on December 31, 2007 and continue until the position is filled.

CALIFORNIA INSTITUTE OF TECHNOLOGY
Division of Engineering and Applied Science
Caltech is an Equal-Opportunity/Affirmative-Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.

UNT UNIVERSITY OF NORTH TEXAS
Discover the power of ideas

Evolutionary Biology and Limnology Positions

The Department of Biological Sciences at the University of North Texas (UNT) seeks to fill two tenure-track positions at the assistant professor level. A doctoral degree in biology, environmental science, or a closely related field is required. Postdoctoral experience is preferred. Successful candidates' duties will include teaching at the undergraduate and graduate levels, and the development of a strong, well-funded research program that ties closely to ongoing interdisciplinary research activities in the department. The first position is for an **Evolutionary Biologist**, and requires research interests and experiences addressing field-based evolutionary questions in plant or animal systems using modern molecular population genetics techniques to explore central concepts in population genetics, phylogenetics, ecology and/or conservation biology. The second position is for a **Limnologist**, and requires research interests and experiences addressing how biological, chemical and/or physical stressors induced by large metropolitan populations in water-limiting conditions alter normal lake, reservoir, river and/or stream ecosystems.

UNT, with over 34,000 students, is located in the Dallas-Fort Worth metropolitan area and offers doctoral degrees in 50 different areas including biology, biochemistry, molecular biology, and environmental science. Excellent research facilities, competitive salary and start-up funds are available. More information regarding the department may be obtained by visiting our website (**www.biol.unt.edu**). Interested individuals must send a letter of application, statement of research and teaching interests, the names and contact information of three references, and *Curriculum Vitae*, preferably electronically, to: **Dr. Sam Atkinson, Department of Biological Sciences, PO Box 310559, University of North Texas, Denton, TX 76203-0559, e-mail: atkinson@unt.edu, phone: 940-565-2694.** Please indicate which position you are applying for in the application letter. For full consideration complete applications must be received by **November 26, 2007**.

UNT is an Equal Opportunity/Affirmative Action Institution committed to diversity in its employment and educational programs, thereby creating a welcoming environment for everyone.

NORRIS COTTON CANCER CENTER
a component of DARTMOUTH HITCHCOCK MEDICAL CENTER

FACULTY POSITION – BREAST CANCER
DARTMOUTH MEDICAL SCHOOL

Norris Cotton Cancer Center, a National Cancer Institute-designated comprehensive cancer center at Dartmouth Medical School and the Dartmouth-Hitchcock Medical Center, invites applications for a full-time, tenure-track, faculty appointment in basic or translational research relevant to breast cancer. In association with extensive clinical research efforts of our Comprehensive Breast Program, we conduct a broad range of fundamental laboratory and population-based research, emphasizing innovative, collaborative studies into the causes, treatment, and prevention of breast cancer. We seek candidates with interests in stem cell biology, tumor micro-environment, and molecular therapeutics; but outstanding candidates with interests in other relevant aspects of breast cancer are encouraged to apply.

Norris Cotton Cancer Center has a strong commitment to understanding the molecular basis for cancer, clinical and translational research, and the development of advanced interventional therapies. For more information on our research portfolio, visit our website at **http://www.cancer.dartmouth.edu/research/index.shtml**.

Exceptional candidates at any level are encouraged to apply. Candidates for appointment at the Assistant Professor level must show evidence of productive research accomplishments. Candidates for Associate or Full Professor must have a currently funded research program and a track record of federal funding. Please submit a curriculum vitae, a description of current and future research plans, copies of recent representative publications, and arrange to have three letters of recommendation submitted to: **Charles N. Cole, PhD, c/o Andrea Tillotson, Norris Cotton Cancer Center, One Medical Center Drive, HB 7920, Lebanon, NH 03756.** Review of applications will begin on **December 1, 2007** and will continue until the position is filled.

Dartmouth is an Affirmative Action/Equal Opportunity Employer and encourages women and minority candidates to apply.

Assistant/Associate Professor, Respiratory Viruses

The Division of Infectious diseases in the Department of Pediatrics at Emory University School of Medicine invites applications for a tenure-track faculty position at the Assistant or Associate Professor level. Priority will be given to individuals with demonstrated research interests in molecular virology and/or pathogenesis of respiratory viruses. Applicants must have a Ph.D., M.D. or equivalent degree with postdoctoral experience and a strong publication record. The successful candidate is expected to establish a competitive independent research program and participate in graduate student teaching. Laboratory space in the new Emory Children's Center building will be available along with competitive start-up funds and salary packages. Applicants at the Associate Professor level are expected to have a record of sustained extramural funding.

Please submit Curriculum Vitae, a statement of research interests, and the names and addresses of three references to **Dr. Richard K. Plemper rplempe@emory.edu; Department of Pediatrics, 2015 Uppergate Drive, Atlanta, GA 30322.**

Emory University is an EEO/AA employer.

EMORY UNIVERSITY SCHOOL OF MEDICINE

ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Plant Systems Modeling
School of Integrative Biology

We seek an outstanding early career scientist with a background in mathematical modeling of plant biological systems for a full-time, tenure-track faculty position at the assistant professor level in the Department of Plant Biology. Exceptional candidates at the associate or full professor level may be considered. Candidates must have a Ph.D. in plant sciences or related field and experience in mathematical modeling of biological systems. The ideal candidate would be a plant scientist with background in design of mechanistic models for forecasting plant productivity and research interest in plants as biofuel feedstocks. The successful candidate would be expected to be an integral part of the Energy Biosciences Institute and would receive funding to develop ~50% of their research effort within the Institute's mission with a focus on the development of new models and approaches to forecast productivity of lignocellulosic feedstocks globally. The candidate must also develop an externally funded research program to model plant systems, which could range from the molecular to the ecosystem level.

The successful candidate would become part of a dynamic and well-established biology and agriculture faculty, as well as a broadly based genomics community. The position involves both graduate and undergraduate instruction including participation in the development of new bioenergy curriculum. The proposed starting date is August 16, 2008. Salary is commensurate with qualification.

To ensure full consideration, applicants should submit a CV, a statement of research and teaching interests, and the names and contact information of three references no later than **January 11, 2008**. Applicants may be interviewed before the closing date, however, no hiring decision will be made until after that date. Please send application materials, including email address, to the **Plant Systems Modeling Search Committee, School of Integrative Biology, University of Illinois, 286 Morrill Hall, 505 South Goodwin Ave., Urbana, IL 61801 (phone: 217/333-3044; fax: 217/244-1224; email: sib@life.uiuc.edu)**.

The University of Illinois is an Affirmative Action, Equal Opportunity Employer. Minorities, women, and other designated groups are encouraged to apply.

American Cancer Society

Postdoctoral Fellowship Awards in the Early Detection of Cancer

CANARY FOUNDATION
Stopping Cancer Early – The Best Possible Investment

Canary Foundation, in partnership with the American Cancer Society, is extending its postdoctoral fellowship program focused on **studies towards development of strategies for the early detection of cancer**. Research should be directed at new approaches to improve clinical methods for the screening of primary tumors and/or metastases.

Awards will be 3 years with stipends of $40,000, $42,000, and $44,000 per yr, plus an annual $4,000 institutional allowance. Based upon availability of funds and scientific merit of the applications, it is anticipated that up to 5 awards will be made. To restrict funding to full 3 year fellowships, applicants may at the time of application, have had no more than 2 years of research experience beyond their terminal degree (MD or PhD). Applicants must be US citizens or permanent residents working with an accomplished mentor at a non-profit institution. Awardees will be asked to attend the "Realizing the Promise" Early Detection Symposium May 20-22, 2008.

Deadlines: Letter of intent: **January 16, 2008**; Application: **February 20, 2008**. For information regarding policies, submission of the letter of intent, or to obtain an application, go to the ACS website **www.cancer.org/research**. To learn about the Canary Foundation, visit **www.canaryfoundation.org**. For inquiries, contact **William Phelps, PhD** at **404-929-6835** (**william.phelps@cancer.org**) or **Michael Melner** at **404-327-6528** (**michael.melner@cancer.org**).

Imperial College London

100 years of living science 100

Faculty of Natural Sciences
Department of Life Sciences
Division of Molecular Biosciences

Lecturer/Senior Lecturer in Experimental Systems Biology

Salary range: £38,880 - £43,420 for Lecturers, £47,960 minimum for Senior Lecturer

Imperial College is ranked in the top ten universities of the world, according to the 2006 Times Higher Education Supplement league tables.

Applications are invited for a post in Experimental Systems Biology at Lectureship or Senior Lectureship level in the Division of Molecular Biosciences within the Department of Life Sciences, Imperial College London. The Division is housed in state-of-the-art laboratories on the South Kensington Campus. Further information about the Division can be found at the following website: http://www.imperial.ac.uk/molecularbiosciences

A major strategic aim of the Division is to understand at the molecular level cellular processes as integrated systems including mechanistic details of individual components that constitute the system. The Division hosts the newly established Imperial College Centre for Integrative Systems Biology (CISBIC; www.imperial.ac.uk/cisbic), which is supported by BBSRC and EPSRC and led by Professor Jaroslav Stark. CISBIC has exemplary research programmes focused around analysis of the innate immune response to bacterial pathogen infection based on a set of three interlinked projects, each addressing fundamental issues in systems biology and each involving closely interacting teams of biological and numerical researchers.

To develop further the activities of CISBIC, we are seeking to recruit a highly-motivated Lecturer/Senior Lecturer in the area of experimental systems biology. We are seeking candidates that have an understanding of the challenges of integrating biological and numerical research in the wider context of biological problems that can be studied by a systems biology approach.

You will also be expected to participate fully in the teaching and administrative activities of the Division. To make informal enquiries about the post please contact Professor Paul Freemont, e-mail: p.freemont@imperial.ac.uk

An application form, further particulars including a job description and person specification can be obtained from the following link:

http://www.imperial.ac.uk/employment/academic

Completed application forms should be e-mailed to c.simmons@imperial.ac.uk or posted to Ms Coralie Simmons, Division of Molecular Biosciences, Department of Life Sciences, Faculty of Natural Sciences, Imperial College London, Flowers Building, South Kensington, London SW7 2AZ.

Closing date: 8 November 2007 at 12 noon.

Interview date: early December 2007.

Valuing diversity and committed to equality of opportunity

POSITIONS OPEN

FACULTY POSITION in NUTRIENT/GENE INTERACTIONS and HEALTHY AGING
Linus Pauling Institute, Oregon State University

The Linus Pauling Institute at Oregon State University invites applications for a tenure-track or tenured, full-time faculty position in its newly created Healthy Aging Program. The successful candidate will be expected to establish or maintain a competitive research program focused on studying the role of diet or micronutrients in influencing cellular, genetic, and physiological function during aging. Of particular interest is research on the interactive effects of nutritional factors on genetic or epigenetic imprinting that ultimately influence healthy aging. Though this position has a primary research focus, the successful candidate is also expected to contribute to undergraduate or graduate teaching and academic service appropriate with faculty rank. See the full position announcement and application instructions at **website: http://jobs.oregonstate.edu.** For additional information, please contact: **Barbara McVicar, e-mail: barbara.mcvicar@oregonstate.edu, Linus Pauling Institute, Oregon State University, 571 Weniger Hall, Corvallis, OR 97331.** *OSU is an Affirmative Action/Equal Opportunity Employer.*

POSTDOCTORAL FELLOW in LUNG TRANSPLANT RESEARCH
Children's Hospital

Boston is looking for a Postdoctoral Fellow to work in the Division of Respiratory Diseases, Perlmutter Laboratory. The candidate should have experience in transplant immunology and/or small animal surgery.

Qualified applicants should send their curriculum vitae to: **Dr. Gary Visner, Director, Lung Transplant, Children's Hospital, 300 Longwood Avenue, HU-268, Boston, MA 02115** or by **e-mail: gary.visner@childrens.harvard.edu.**

NEUROSCIENCE POSITIONS

The Emory University Interdepartmental Program in Neuroscience and Behavioral Biology (NBB) seeks a nontenure-track **LECTURER** with formal graduate training in neuroscience and proven scholarship in neuroethics. The candidate must have a Ph.D. and a record of excellence in undergraduate teaching. The successful candidate will help develop a neuroethics curriculum, teach NBB courses, and participate in a required writing intensive senior capstone seminar. There will also be the opportunity to become an active member in the university-wide initiative in neuroscience, human nature, and society. Applications should include curriculum vitae, summary of past research, teaching profile, and three reference letters that specifically address the applicant's teaching experiences and abilities. Applications and references should be addressed to: **Paul Lennard, Chair of the Neuroethics/Neuroscience Search, c/o Neuroscience and Behavioral Biology Program, 1462 Clifton Road, Suite 304, Atlanta, GA 30322; e-mail: nbbsearch@emory.edu.** Review of applications will begin January 15, 2008. *Emory is an Equal Opportunity/Affirmative Action Employer.*

ION CHANNEL ELECTROPHYSIOLOGIST. Position available within Center for Neuroscience and Regeneration Research, Yale University, for **PATCH CLAMP PHYSIOLOGIST** to join multidisciplinary research group studying molecular pathophysiology of sodium channels (see *Proc. Natl. Acad. Sci.* **103:** 8245-8250, 2006; *Journal of Physiology* **579:**1-14, 2007). Expertise with patch-clamp techniques is essential, and experience studying voltage-gated sodium channels is desirable. Incumbent will interact closely with molecular and cell biologists in a highly collaborative setting. Send curriculum vitae, three letters of reference, and statement of interest to: **Stephen G. Waxman, M.D., Ph.D., Chair, Department of Neurology, LCI 708, Yale University School of Medicine, P.O. Box 208018, New Haven, CT 06520-8018.** *Qualified women and members of underrepresented minority groups are encouraged to apply. Affirmative Action and Equal Opportunity Employer.*

POSITIONS OPEN

UNIVERSITY OF NOTRE DAME

The University of Notre Dame invites applications for a dynamic leader and visionary to serve as **DEAN, COLLEGE of SCIENCE**. The College contains 12 research centers and includes 140 faculty members in four academic departments: Biology, Chemistry and Biochemistry, Mathematics, and Physics. Supported by a $70 million science teaching facility, $43 million in extramural funding, and significant imminent institutional investments, the College aims to strengthen and expand its research program. To apply, please send cover letter and curriculum vitae via e-mail only to **Lisa Prigohzy-Milius** via e-mail: nd-science@presidiosearch.com.

FACULTY POSITION at the UNIVERSITY of MONTANA
Center for Biomolecular Structure and Dynamics

The Center for Biomolecular Structure and Dynamics (CBSD) welcomes applications for a tenure-track position at the level of **ASSISTANT PROFESSOR in the DIVISION of BIOLOGICAL SCIENCES.** We seek a talented and innovative investigator in the field of biophysics, structural biology, or mechanistic biochemistry, with research interests in hydrogen metabolism with application to biocatalytic and biomimetic systems. The CBSD derives its multidisciplinary faculty from the biological, chemical, computational, and pharmacological sciences, focused on the exploration and elucidation of biological processes at the molecular and atomic level. The successful candidate will be expected to develop a vigorous, extramurally funded research program and exhibit a strong commitment to teaching within the area of biochemistry, as well as mentorship at the undergraduate and graduate levels. Applicants must have a Ph.D. or equivalent degree, a demonstrated record of graduate and postdoctoral research excellence, and teaching effectiveness. Applicants should send (1) curriculum vitae with a description of research accomplishments, (2) a detailed statement of future research plans, and (3) teaching interests, together with the names of three potential references to:

CBSD Faculty Search Committee
c/o Roslyn Pinson
Center for Biomolecular Structure and Dynamics
Davidson Honors College 002
University of Montana
32 Campus Drive #1049
Missoula, MT 59812-1049

Applications, in the form of a PDF document, may be sent by **e-mail: cbsd@umontana.edu.**

Review of applications will begin on January 1, 2007. The Center is interested in hiring a candidate who will enhance the ethnic and gender diversity of its faculty. *UM is an Affirmative Action/Equal Opportunity Employer/ADA/Veterans Preference Employer and the recipient of an ative National Science Foundation Partnership for Comprehensive Equity award. This material is available in an alternative format upon request.*

ASSISTANT PROFESSOR, BIOCHEMISTRY

Metropolitan State University, St. Paul/Minneapolis, seeks a tenure-track faculty in biochemistry. Qualifications: Ph.D. in biochemistry, chemistry, biology, or related field by time of appointment; ability to teach a broad range of undergraduate science courses; successful teaching experience. Apply by December 14, 2007. For description of position, qualifications, and application process, go to **website: http://www.metrostate.edu/hr/jobs.cfm.**

A member of the Minnesota State Colleges and Universities System.

Affirmative Action/Equal Employment Opportunity.

POSITIONS OPEN

FACULTY OPENING in LANDSCAPE ECOLOGY
University of Illinois at Chicago
845 W. Taylor Street M/C 066
Chicago, Illinois 60607

The Department of Biological Sciences **(website: http://www.uic.edu/depts/bios/)** at the University of Illinois at Chicago (UIC) invites applications for an **ASSISTANT PROFESSOR** position. This tenure-track faculty position, which includes a joint appointment with UIC's Institute for Environmental Science and Policy **(website: http://www.iesp.uic.edu),** starts August 16, 2008. Applications from outstanding individuals at more senior levels **(ASSOCIATE, FULL PROFESSOR)** may also be considered.

Research areas of particular interest include, but are not limited to, multiscale approaches to the study of (1) patterns of land use and the functioning, sustainability, or restoration of ecosystems; (2) biogeochemical or hydrologic processes and their relationship to ecological systems; and (3) invasive species ecology. Relevant research areas are not limited to these topics, and **LANDSCAPE ECOLOGISTS** with research accomplishments and interests in other areas are encouraged to apply. Candidates must have a Ph.D., significant postdoctoral experience, and a demonstrated record of research accomplishments. They will be expected to establish a vigorous, externally funded research program, teach effectively in the Department's undergraduate and graduate programs, and actively participate in UIC's new National Science Foundation-funded Integrative Graduate Education and Research Traineeship interdisciplinary doctoral training program called LEAP (Landscape, Ecological, and Anthropogenic Processes), **website: http://www.leap.uic.edu.**

Located in the heart of Chicago, UIC is one of the nation's leading research universities. Numerous opportunities exist for collaborative research in landscape ecology across disciplines at UIC and with colleagues and institutions throughout the Chicago region.

For fullest consideration, please submit electronically at **website: http://www.uic.edu/depts/bios/** by December 15, 2007. *UIC is an Affirmative Action/Equal Opportunity Employer.*

FACULTY POSITION
Department of Chemistry
Georgia State University

The Department of Chemistry at Georgia State University anticipates two tenure-track faculty position openings at the **ASSISTANT/ASSOCIATE PROFESSOR** level for fall 2008. The Department seeks outstanding candidates capable of achieving excellence in research and teaching. Applicants must have a Ph.D. or equivalent degree with postdoctoral training. Although outstanding scientists in all areas of chemistry are encouraged to apply, preference will be given to candidates with a research focus in biochemistry or computational biophysical chemistry. There is an option for a joint appointment in the Biology Department. The Department of Chemistry offers a highly intellectual, collaborative, and continually growing environment, with 18 full-time, tenured or tenure-track faculty and more than 60 Ph.D. and 30 M.S. students. Applicants must submit a research plan, a statement of teaching objectives that demonstrates a commitment to education, curriculum vitae, reprints of at most three recent research publications, a two-page summary of research accomplishments, and arrange to have three letters of recommendation sent to: **Prof. D.W. Dixon, Faculty Search Committee Chair, Department of Chemistry, Georgia State University, P.O. Box 4098, Atlanta, GA 30302-4098.** Reviewing of applications will start on November 7, 2007, and will be open until the position is filled. *Georgia State University is an Affirmative Action/Equal Employment Opportunity Employer.*

ASSISTANT PROFESSOR OF BIOCHEMISTRY

The Dept of Biochemistry at the Albert Einstein College of Medicine, Yeshiva University, is seeking applications for tenure-track Assistant Professors. Applicants should be developing novel and innovative approaches to fundamental questions of biological chemistry that will impact human health.

The Albert Einstein College of Medicine is undergoing a substantial expansion with the inauguration of a new research building for genetic and translational research this fall. Research interests of applicants should complement those of the existing faculty, including programs with broad applications to biochemistry, chemical biology and translational biochemistry. Specific areas of interest include, but are not limited to, small molecule inhibitor design or selection, computational/experimental approaches to small molecule/ligand-macromolecular binding, genomic or proteomic approaches to metabolism and targets, systems biology and epigenetics/biochemistry interface.

Candidates are expected to have a PhD or MD degree, postdoctoral experience and a strong record of accomplishments.

Applicants should send a curriculum vitae and a 4-page summary of their intended research plans as a single pdf file to: **BCsearch@medusa.biocaecom.yu.edu** The deadline for receipt of applications is December 15, 2007. Letters from three or more references should be sent to the same email address. Other correspondence may be addressed to: **Search Committee, Dept of Biochemistry, Albert Einstein College of Medicine, Jack & Pearl Resnick Campus, 1300 Morris Park Avenue, Bronx, NY 10461.** EOE

ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY

Faculty Recruiting in Cancer Research

The Jackson Laboratory

The Jackson Laboratory, a mammalian genetics research institution and NCI-designated Cancer Center, has launched a major faculty expansion in Cancer Research.

We encourage applications for positions at the Assistant, Associate and Full Professor level, especially from those with an interest in interdisciplinary and/or translational approaches. Candidates should have a Ph.D., M.D., or D.V.M., and have completed postdoctoral training with a record of research excellence, and they must have the ability to develop a competitive, independently-funded research program that takes advantage of the mouse as a genetic model for human cancer.

We offer a unique scientific research environment, including excellent collaborative opportunities within our faculty of 37 principal investigators, unparalleled mouse genomic resources, outstanding core scientific support services, highly successful postdoctoral and predoctoral training programs, and a major scientific meeting center, featuring courses and conferences centered on mouse models.

For more information, go to: www.jax.org

Applicants should send a curriculum vitae and a concise statement of research interests and plans, and arrange to have three letters of reference sent to: **facultyjobs@jax.org**

Review of applications will begin in January of 2008.

The Jackson Laboratory is an EOE/AA employer.

The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609

www.jax.org

Post Doctoral Position - MRI Applications in Immune Mediated Tumor Response

This position is aimed at investigating MR imaging of immune mediated tumor responses with the goal of translating methodologies developed in small animal models to the clinic. We are interested in an individual who is firmly grounded in NMR theory and practice with an interest in applications in immunological approaches to cancer therapy including antibodies, immunocytokines, T-cells, dendritic cells, and small molecule drugs. This work will involve development and application of various MR methodologies in the Biological Imaging Center and Caltech Brain Imaging Center (**http://bioimaging.caltech.edu/**) in coordination with researchers and physicians in the Division of Cancer Immunotherapeutics and Tumor Immunology at City of Hope (**http://www.cityofhope.org/citi**).

Interested applicants with experience in small animal MRI should email, FAX, or mail a biosketch including names, addresses, and email addresses of three references to

Russell E. Jacobs
m/c 139-74 Caltech
1200 E. California Blvd
Pasadena, CA 91125-7400
rjacobs@caltech.edu
Phone: (626) 395-2863
Fax: (626) 449-5163

The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer and encourages the applications of qualified women, minorities, veterans and disabled persons.

PENNSTATE University Park

Head, Department of Biochemistry and Molecular Biology

Penn State invites applications and nominations for the position of Head of the Department of Biochemistry and Molecular Biology. We are seeking an individual with a vibrant ongoing research program, strong interpersonal skills, a commitment to excellence, and a commitment to diversity and a supportive environment for faculty and students, to provide energetic and able leadership for the Department. The Department has 40 faculty members whose research explores a wide spectrum of biological questions at the molecular level. This research is supported by extensive external funding. The Department has vigorous undergraduate and graduate educational programs and participates in a number of interdisciplinary graduate programs. The Department interfaces with other excellent departments in the Eberly College of Science and has extensive collaborations with other life science researchers across Penn State, including at the Hershey Medical Center, as well as across the nation and around the world. Continued growth and excellence in life sciences is a priority of Penn State and the Eberly College of Science. The incoming head will have a number of faculty lines and other resources to enhance existing areas of expertise and develop new frontiers. Further information about the Department may be found at http://www.bmb.psu.edu.

The position is available for Fall 2008. Credentials appropriate to the rank of tenured full professor are required. Review of applications and nominations will begin November 15, 2007 and will continue until the position is filled. Applications, including curriculum vitae and the names of three references, and nominations may be submitted via email to mlbl@psu.edu or mailed to: BMB Head Search Committee, The Pennsylvania State University, Eberly College of Science, 512 Thomas Building, University Park, PA 16802.

Penn State is committed to affirmative action, equal opportunity and the diversity of its workforce.

PENN STATE ***Making Life Better***

POSITIONS OPEN

PLANT ECOLOGY
Harvard University

The Department of Organismic and Evolutionary Biology (OEB) at Harvard University invites applications for a tenure-track faculty position in plant ecology with an emphasis in the area of global change. We seek to appoint an individual who studies the ecology of plants and/or plant-organism interactions in terrestrial, aquatic, or marine environments at the physiological, population, community, or ecosystem level. We are especially interested in individuals who conduct rigorous field observations and/or experiments that advance our understanding of how climate change, habitat transformation, species introductions, and species extinctions are affecting ecosystems at local, regional, and global scales. Applicants will be expected to develop an innovative research program and contribute to teaching at the undergraduate and graduate levels. Applications from, or information about, female and minority candidates are encouraged. This search is part of a broader initiative to develop comprehensive research programs in plant biology and ecology at Harvard University. The Department has strong linkages to a number of allied institutions, including the Harvard Forest, Arnold Arboretum, Harvard University Herbaria, Harvard Museum of Comparative Zoology, and Harvard Center for the Environment.

Applicants should submit the following application materials online to **website: http://www.lsdiv.harvard.edu/oeb/facultysearch:** curriculum vitae, statements of research and teaching interests, representative publications, and arrange for three references to be uploaded to the website. Letters of nomination from third parties are also welcome and may be sent via e-mail to **Paul R. Moorcroft, Professor of Biology, c/o Katie Parodi, e-mail: kparodi@oeb.harvard.edu.** Review of applications will begin on December 1, 2007.

Further information about OEB is available at **website: http://www.oeb.harvard.edu;** information about the Plant Biology Initiative at Harvard can be found at **website: http://www.pbi.fas.harvard.edu.**

Harvard University is an Affirmative Action/Equal Opportunity Employer.

RESEARCH TECHNOLOGIST

The Department of Anatomy and Physiology invites applications for the position of Research Technologist. The successful applicant will maintain laboratory resources; prepare DNA and total RNA isolation; analyze and summarize data collected from experiments, maintain accurate records on all aspects of the investigator's rodent colonies, including production and performance data, veterinary health reports, and Institutional Animal Care and Use Committee records. Occasional work on weekends is required. B.S. degree required; American Association for Laboratory Animal Science Laboratory Animal Technician or Laboratory Animal Technologist certification is preferred. Screening of applications will begin October 29, 2007, and continues until position is filled. Material to be submitted: letter of application, current resume, and three references. E-mail material to **e-mail: bthomps@vet.k-state.edu.** *Kansas State University is an Equal Opportunity, Affirmative Action Employer. KSU actively seeks diversity among its employees.*

A **POSTDOCTORAL POSITION** is available in the Laboratory of **Dr. Aziz Sancar** in the Department of Biochemistry and Biophysics at the University of North Carolina at Chapel Hill to study the interface between human nucleotide excision repair and the DNA damage checkpoints. Applicants with a strong working background in biochemistry and molecular biology are encouraged to apply. Please contact me directly to apply or for more information:

Aziz Sancar
University of North Carolina at Chapel Hill
Department of Biochemistry and Biophysics
CB #7260
Chapel Hill, NC 27499-7260
E-mail: aziz_sancar@med.unc.edu

POSITIONS OPEN

ASSISTANT/ASSOCIATE PROFESSOR in HUMAN GENETICS
University of Missouri-Kansas City
School of Medicine

Position overview: The Department of Basic Medical Science seeks outstanding candidates for two full-time, tenure-track, faculty (Assistant/Associate Professor) positions at the University of Missouri-Kansas City (UMKC) School of Medicine. Successful candidates are expected to work closely with **Dr. Hong-Wen Deng** in developing a comprehensive research program in genetic studies of complex human diseases at UMKC. This growing Program will encompass all relevant research fields related to identifying and characterizing genes and their functional contribution to complex human disorders, which may include statistical genetics, molecular genetics, gene functional studies, functional genomics and proteomics, et cetera. This position is immediately available, and the qualified candidate is expected to start his/her work at UMKC by September 1, 2008, at the latest. Generous startup packages and competitive salaries are available.

Qualifications: Applicants must have a doctoral degree in a relevant academic discipline, postdoctoral experience, a solid publication record of original research in peer-reviewed journals, and significant potential to develop an independent, extramurally funded research program. Research experience in at least one of the following areas is preferred: population based association studies of complex human diseases, population genetics, microarray data analysis, proteomics, and gene functional analysis. Research experience in human osteoporosis and obesity is a plus.

Effective September 1, 2007, all final candidates will be required to successfully pass a criminal background check prior to beginning employment.

Contact information: Interested applicants should submit curriculum vitae and the names, addresses, e-mail address, and telephone numbers of three references to **e-mail: gilmoreac@umkc.edu.**

Application deadline: Applications will be accepted until the position has been filled.

UMKC is an Equal Opportunity Employer/Educational Institution and candidates of all backgrounds are encouraged to apply.

Louisiana State University Health Sciences Center in New Orleans, Louisiana, has an immediate opening for a **POSTDOCTORAL RESEARCHER.** The overall duties of the researcher in this position are to plan, organize, and conduct highly independent research on two projects: (1) understanding the role of Nischarin in breast cancer cell migration and invasion; and (2) studying the role of Nischarin in tumor progression and metastasis using animal models. For further information see **website: http://www.medschool.lsuhsc.edu/biochemistry/faculty_detail.asp?id=1121.** Applications are sought from highly motivated individuals with strong background in molecular and cell biology. Candidates must have a Ph. D. in biochemistry, molecular or cellular biology, or health-related field. Desire demonstrated experience in molecular techniques such as gene cloning, gene expression, and mammalian cell transfections. Experience with animals is a plus. Interested candidates should send curriculum vitae, a summary of research statement and names, telephone numbers, and e-mail addresses of three references to: **Dr. S.K. Alahari, Department of Biochemistry and Molecular Biology, Louisiana State University Health Science Center, Clinical Science Research Building, New Orleans, LA 70119. E-mail: salaha@lsuhsc.edu.** *LSUHSC is an Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

ASSISTANT PROFESSOR. The Pennsylvania State University invites applications for tenure-track positions in the Department of Bioengineering at its University Park campus. Applicants are expected to have a Ph.D. and postdoctoral training in bio/biomedical engineering, chemical or electrical engineering, biophysics, or a related discipline. The Department has a 30-year history and research strengths in cardiovascular bioengineering, cell and molecular biomechanics, biophotonics, biomaterials, neural engineering, and biomedical imaging. For more details, visit **website: http://bioeng.psu.edu.** Outstanding candidates in all areas of bioengineering will be considered, however, preference will be given to candidates with expertise in either of the following three areas. Computational biology: computer simulations and/or mathematical modeling to elucidate biological function at the cellular and/or molecular level. Approaches such as kinetic or network modeling and applications to intracellular signaling are of particular interest. Medical imaging: small animal imaging using MRI, ultrasound, or optical coherance tomography. A focus on organ specific pathophysiology or a specific disease is desirable. The ability to interface with existing biomedical imaging faculty in the Department is highly desirable. Micro/nano scale medicine: development and application of nanoscience, microfabrication, and/or materials science tools to investigate fundamental or applied questions in cellular and molecular function in health and disease. Candidates are expected to attract extramural funding and contribute to departmental teaching at the undergraduate and graduate levels. In addition to departmental resources, additional facilities and potential for collaboration exist at Penn State in the Huck Institute for Life Sciences, the Materials Research Institute, and Hershey Medical School. Send curriculum vitae, statement of research and teaching objectives, three reprints, and names of three references to: **Dr. Herbert H. Lipowsky, Professor and Head, Department of Bioengineering, The Pennsylvania State University, 205 Hallowell Building, University Park, PA 16802,** or **e-mail: hhlbio@engr.psu.edu.** *Penn State is committed to Affirmative Action, Equal Opportunity and the diversity of its work force*

ASSISTANT PROFESSOR
The Division of Basic Biomedical Sciences
Sanford School of Medicine
The University of South Dakota

The Division of Basic Biomedical Sciences at the Sanford School of Medicine of the University of South Dakota invites applications for a tenure-track faculty position at the Assistant Professor level. Exceptional applicants at higher levels may also be considered. Applicants should have a Ph.D. and/or M.D., or equivalent degree, and postdoctoral experience. Successful candidates will be expected to develop an independent, externally funded research program in the area of protein quality control, particularly as it relates to the genesis and/or treatment of prevalent diseases. The Division has set a priority to expand research in the area of protein quality control. Preference will be given to applicants whose research complements the already existing strengths in protein folding, molecular chaperones, targeted proteolysis, and signal transduction. The successful candidate will also be expected to participate in teaching undergraduate, graduate, and medical students. Excellent startup funds, state-funded salary commensurate with experience and modern research facilities in the new Lee Medical Building, Vermillion, South Dakota, will be provided. Application should include curriculum vitae, representative reprints, summary of past experience, statement regarding research interests and future plans, as well as contact information of three references. All materials should be sent to the University of South Dakota online employment **website: http://yourfuture.sdbor.edu.** Review of applications will begin on November 11, 2007, and continue until position is filled. *Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

COMPUTATIONAL GENOMICS/ PHYLOGENOMICS SEARCH

The University of Florida, Department of Botany (website: http://web.botany.ufl.edu/), invites applications for a full-time, nine-month, tenure-track position in computational genomics/phylogenomics at the level of **ASSISTANT PROFESSOR** to begin August 2008. Candidates with expertise and research interests in plant phylogenetic relationships, evolutionary, and/or population genomics are desired. A strong commitment to both undergraduate and graduate teaching and training is required. The candidate will contribute to teaching in the areas of introductory biology, plant systematics, and phylogenetics, and will develop a course in computational phylogenomics. The successful candidate is expected to maintain an active, high-level, interdisciplinary, and extramurally funded research program. Ph.D. degree required. Interest applicants should submit curriculum vitae, statement of research interest and teaching philosophy, a selection of no more than three reprints, and arrange three letters of recommendations to: **Computational Genomics/Phylogenomics Search Committee,** e-mail: pdwill@botany.ufl.edu. Application materials and reference letters should be received by January 7, 2008. *The University of Florida is an Equal Opportunity Institution.*

CHAIR, BIOLOGY DEPARTMENT

Lamar University seeks an energetic and productive Chair for the Department of Biology. Lamar University is a state-supported institution with approximately 10,000 students located in Beaumont, Texas, close to the Gulf of Mexico and 90 minutes from Houston. A part of the College of Arts and Sciences, the Department offers undergraduate degrees in environmental science and medical technology as well as graduate and undergraduate degrees in biology. Applicants must possess an earned Doctorate in biological science, and prior administrative experience is strongly preferred.

A documented record of scholarship is required for this senior level appointment. More information about the position is available on the departmental website. Anticipated starting date of fall 2008 with a review of applications to begin December 1, 2007. Applicants should send a letter of interest which includes statements of administrative style, teaching philosophy, and research interest along with current curriculum vitae, and names/contact information of at least three references to:

Biology Chair Search
c/o Human Resources
Lamar University
P.O. Box 11127
Beaumont, TX 77710

Lamar University is a member of the Texas State University System and an Affirmative Action/Equal Opportunity Institution.

UNIVERSITY of CALIFORNIA, RIVERSIDE

Three **POSTDOCTORAL POSITIONS** are available immediately in the Department of Biochemistry at the University of California, Riverside, to study the biochemistry and molecular biology of the interaction between diet, drugs, and lifespan. The studies will use *Drosophila*, annual fish, and mice for a chemical-genomic investigation of the cross-species role of small molecule therapeutics and signaling pathways in longevity. A strong foundation in biochemistry and molecular biology, and experience in one of the experimental systems is preferred. Please submit your curriculum vitae and a list of three references electronically to **Stephen Spindler, Ph.D. (e-mail: spindler@ucr.edu),** before December 15, 2008.

POSITIONS OPEN

FACULTY POSITIONS in BIOLOGY
The University of Washington

The University of Washington's Department of Biology has two open tenure-track faculty positions. We welcome applicants in both core and interdisciplinary areas of biology but have particular interest in areas of cellular, molecular, and physiological levels of organization in plants or animals. A record of outstanding achievement, a promising research program, and a commitment to teaching are more important than the specific research area. Our consolidation of Botany, Zoology and Undergraduate Biology Programs into a single unit expands opportunities for new projects and interdisciplinary initiatives. Information about the Department is available at **website: http://www.biology.washington.edu.**

Appointments at the **ASSISTANT PROFESSOR** rank are anticipated. Appointments at the **ASSOCIATE or FULL PROFESSOR** rank may be considered for candidates who have demonstrated a commitment to mentoring underrepresented students in the sciences. Applicants must have earned a Doctorate by the date of appointment.

Please apply online at **website: http://www.biology.washington.edu/fachires/** and submit a cover letter, curriculum vitae, sample reprints, statements of research and of teaching interests, and names of at least three references. Applications received by November 1, 2007, will be given priority.

University of Washington faculty engage in teaching, research, and service. The University of Washington, a recipient of the 2006 Alfred P. Sloan award for Faculty Career Flexibility, is committed to supporting the work-life balance of its faculty. *The University is building a culturally diverse faculty and staff and strongly encourages applications from women, minorities, individuals with disabilities, and covered veterans. The University of Washington is an Affirmative Action, Equal Opportunity Employer.*

FACULTY POSITION in PHARMACOLOGY and TOXICOLOGY
Brody School of Medicine at East Carolina University

The Department of Pharmacology and Toxicology is seeking applications for a tenure-track faculty position from individuals conducting state-of-the-art research in toxicological sciences. Appointment rank is open and dependent upon the applicant qualifications but minimum requirements include a Ph.D. or equivalent degree in pharmacology, toxicology, or a related field with at least two years of postdoctoral experience preferred. The successful candidate will be expected to establish/maintain independent, externally supported research program, participate in the teaching mission, and train graduate students and contribute to service activities. Applications will be reviewed beginning September 30, 2007, and will be accepted until the position is filled. In addition to completing an application online (**website: https://ecu.peopleadmin.com/applicants/**), please submit curriculum vitae, a brief statement of research interests, teaching experience, and the names and e-mail addresses for three professional references to: **Ms. Pam Wynne (e-mail: wynnepa@ecu.edu), Administrative Support Associate, Department of Pharmacology and Toxicology, Room 6S-10, The Brody School of Medicine at East Carolina University, Greenville, NC 27834.** *East Carolina University is an Equal Opportunity Employer and welcomes applications from women and minority candidates.*

POSTDOCTORAL POSITIONS are available at Washington University in St. Louis, Missouri, focusing on lung cancer genetics and chemoprevention. A doctoral degree, experience in statistical genetics, molecular/cell biology, transgenic/knockout animal studies, and strong English communication skills are required. Preference will be given to individuals with previous experience in the respective fields. Interested individuals should send resume to **e-mail: kayec@wustl.edu** with "post doc" on the subject line.

POSITIONS OPEN

CARDIOVASCULAR POSTDOCTORAL FELLOWSHIPS are available in the Cardiovascular Innovation Institute (CII) with a number of investigators comprising a multidisciplinary team evaluating the mechanisms underlying and new therapies for cardiovascular disease. Opportunities exist in the areas of cardiovascular molecular and cell biology, microvascular biology, cell-based therapies, stem cells, biomaterials, inflammation, and cardiovascular medical devices. Those with an interest in translational and/or entrepreneurial activities are encouraged to apply. Candidates will be supported by an interdisciplinary team of fostering mentors within a fully equipped, new state-of-the-art research building located within a large health sciences hospital and research complex. The CII is located in Louisville, a progressive city situated along the scenic Ohio River with a thriving cultural scene and a variety of outdoor recreation opportunities. Please e-mail curriculum vitae in PDF format to **James B. Hoying** at e-mail: jay.hoying@louisville.edu.

MULTIPLE TENURE-TRACK POSITIONS in BIOLOGICAL SCIENCES

As part of a major initiative to strengthen our Department, the Department of Biological Sciences at the University of New Orleans invites applications for multiple, tenure-track positions at the **ASSISTANT PROFESSOR** level in these areas: ecology/evolutionary biology, physiology, and biochemistry/molecular biology. We especially seek applications from broadly trained individuals with research interests that span traditional disciplines within biology. Successful candidates will be expected to develop vigorous, extramurally funded research programs, to fully participate in the Ph.D. program in conservation biology (ecology/evolutionary biology and physiology positions), or in a new interdisciplinary Ph.D. program in biochemistry, and to contribute to undergraduate education. Applicants must have a Ph.D. and postdoctoral experience.

Submit a letter of application stating which position is sought, curriculum vitae, statements of research and teaching interests, and names/contact information for three letters of reference to **Steve Johnson (e-mail: sgjohnso@uno.edu)** or mail to: **Biology Search Committee, Department of Biological Sciences, University of New Orleans, LA 70148; telephone: 504-280-6307; fax: 504-280-6121.** Review of applications will begin December 1, 2007, and continue until all positions are filled. For more information about the Department of Biological Sciences see **website: http://biology.uno.edu/.** *UNO is an Affirmative Action/Equal Opportunity Employer.*

FACULTY POSITION in TOXICOLOGY/CLINICAL CHEMISTRY

Applications are invited for a position in the Department of Chemistry and Biochemistry at Florida International University (FIU) in the area of toxicology, forensic toxicology, or clinical chemistry, with an appointment starting in fall 2008. A Ph.D. and postdoctoral experience are required. Candidates are expected to develop a vigorous and externally funded research program. FIU is a public research extensive university with over 38,000 students located in west-suburban Miami, with a new medical school scheduled to open in 2009. The rapidly growing Department houses 29 faculty and 85 graduate students. Please see **website: http://www.fiu.edu/orgs/chemistry** for more details. Send curriculum vitae, transcripts, research plans, and three letters of reference to: **Toxicology Search Committee, Department of Chemistry and Biochemistry, Florida International University, Miami, FL 33199.** The selection process will begin on December 31, 2007. *FIU is an Equal Opportunity and Affirmative Action Employer.*

The UCSF Fellows Program

Nominations are being solicited for appointment as a 'UCSF Fellow' in a program at the University of California, San Francisco that brings talented young scientists into our diverse and interactive research community. UCSF Fellows independently pursue biomedical research without the obligations of faculty membership or the constraints of a conventional postdoctoral fellowship. Thus, the UCSF Fellows Program provides an alternative or a supplement to traditional postdoctoral study following the M.D. or Ph.D. degree, and an opportunity to establish a creative and successful research program prior to obtaining a faculty position.

UCSF Fellows are independent group leaders who occupy small laboratories adjunct to UCSF faculty; they receive an annual financial award to cover their salary and partially defray the costs of their research program. UCSF Fellows may recruit postdoctoral fellows and are encouraged to seek extramural funds to support research groups of 3-5 members. The UCSF Fellow award is nonrenewable, for a term of five years. See **http://biochemistry.ucsf.edu/~ucsffellows/** for additional details on the program.

A candidate must be nominated by a mentor/advisor who is able to comment in some depth on the accomplishments and future potential of the candidate. The nomination letter should be accompanied by the nominee's curriculum vitae. Subsequently, selected candidates will be asked to arrange for three additional letters of recommendation, and to submit a brief research plan. Nominees working in any area of modern biomedical sciences will be considered. Although the UCSF Fellows Program is eager to consider nominations of all exceptional individuals, we are particularly interested in attracting minorities and women to our campus.

The deadline for letters of nomination is **January 15, 2008**. We anticipate interviewing selected candidates in the spring of 2007, and aim to appoint a new UCSF Fellow to start in the second half of 2008. Nominations should be sent to the attention of:

Dr. Douglas Hanahan
Chair, UCSF Fellows Steering Committee
University of California, San Francisco
c/o The UCSF Diabetes Center
513 Parnassus Avenue, Room HSW1090
San Francisco, California 94143-0534
EM: dh@biochem.ucsf.edu

The UCSF Fellows Program is sponsored by the Sandler Family Supporting Foundation.

MRC Laboratory of Molecular Biology

MRC Laboratory of Molecular Biology, Cambridge

Group Leaders

£37,000 - £47,000 per annum

The MRC Laboratory of Molecular Biology in Cambridge is seeking to recruit Group Leaders in the Structural Studies Division. We are currently building up new areas of research in connection with a move to a new building.

Enthusiastic candidates from any relevant area are encouraged to apply. This includes, but is in no way restricted to crystallography of large complexes, electron microscopy (either tomography or single particle reconstruction) and single molecule biophysics.

The Laboratory provides world-leading infrastructure, long-term funding and a collegial atmosphere that allow scientists to tackle difficult and important problems without the necessity to write grants. Candidates should have a PhD and postdoctoral experience, and an outstanding track record of research accomplishments.

Appointments will be made at either Programme Leader or Programme Leader Track depending on experience and achievements. Your salary will be internationally competitive and commensurate with experience and accomplishments - and is supported by a flexible pay and reward policy; 30 days annual leave entitlement, an optional MRC final salary pension scheme and excellent on-site sports and social facilities.

Informal enquiries and requests for further information can be addressed to either Venki Ramakrishnan, email: ramak@mrc-lmb.cam.ac.uk or Kiyoshi Nagai, email: kn@mrc-lmb.cam.ac.uk

Applications should include a full CV, an outline of current and future research interests and the names and addresses of three professional referees who have agreed to be contacted.

For further information and to apply online please visit our website: http://jobs.mrc.ac.uk or telephone 01793 301154 quoting reference LMB07/646.

Closing date: 30 November 2007.

For further information about the MRC visit www.mrc.ac.uk
The MRC is an Equal Opportunities Employer
'Leading science for better health'

POSITIONS OPEN

INSTITUT PASTEUR

POSTDOCTORAL FELLOWSHIPS
Institut Pasteur, Paris, France

Founded in 1887 by Louis Pasteur and located in the heart of Paris, the Institut Pasteur is a world-renowned private research organization. The Pasteur Foundation of New York is seeking outstanding fellowship applicants. Candidates may apply to any laboratory within 10 Departments: Cell Biology and Infection, Developmental Biology, Genomes and Genetics, Immunology, Infection and Epidemiology, Microbiology, Neuroscience, Parasitology and Mycology, Structural Biology and Chemistry, and Virology. See website for details. Annual package is $70,000 for three years. This is a biannual call for applicants; see website for deadlines. *U.S. citizenship required.*

E-mail: pasteurus@aol.com. Website: http://www.pasteurfoundation.org.

ASSISTANT PROFESSOR in AQUATIC BIOLOGY

The Department of Biology at the University of South Dakota (USD) **(website: http://www.usd.edu/biol/)** invites applications for an Assistant Professor (nine-month, tenure-track) in aquatic biology. We seek an individual with a broad background in aquatic biology, interested in integrative and collaborative research, who will develop a creative externally funded research program, and exhibit excellence in teaching/mentoring of undergraduate and graduate students. Candidates whose research explores the ecology of rivers, streams, riparian systems, or wetlands are especially encouraged to apply. Opportunities for collaboration exist through the USD Missouri River Institute **(website: http://www.usd.edu/mri/).** Ph.D. required; postdoctoral research/teaching experience preferred. Applications must include a cover letter, curriculum vitae, statement of research and teaching interests, and contact information for three professional references. Applications to be submitted online **(website: http://yourfuture.sdbor.edu)** or alternatively, by hard copy to: **Aquatic Biologist Search, Department of Biology, University of South Dakota, 414 East Clark Street, Vermillion, SD 57069.** Questions should be directed to **Dr. Daniel Soluk (e-mail: dsoluk@usd.edu).** Review of applications begins November 26, 2007, and will continue until the position is filled. *USD is an Affirmative Action/Equal Opportunity Employer.*

ASSISTANT PROFESSOR
Developmental Biology

The University of South Carolina Beaufort invites applications for a tenure-track faculty position in developmental biology. Candidates must apply molecular methods in teaching and research and can specialize in any area using any model or nonmodel system, although there is some preference for work with aquatic species. The successful applicant will be expected to teach undergraduate courses in general biology, developmental biology, and genetics. Application procedures: Applicants must complete the Academic Personal Information form online at **website: https://uscjobs.sc.edu,** and are required to submit a letter of application detailing interest in the position and teaching philosophy, curriculum vitae, a copy of transcripts, and at least three letters of recommendation. Items required which cannot be submitted electronically should be mailed to: **Chair, Biology Search Committee, c/o Human Resources, University of South Carolina Beaufort, One University Boulevard, Bluffton, SC 29909.** Review of applications will begin November 2007.

POSITIONS OPEN

ASSISTANT/ASSOCIATE PROFESSOR FACULTY POSITIONS in MICROBIOLOGY, COMPARATIVE ANATOMY, and ANATOMY and PHYSIOLOGY

The Biology Department at Southern Connecticut State University in New Haven, Connecticut, invites applications for three full-time, tenure-track positions.

Microbiology. The successful candidate will teach a general microbiology course for science majors and be responsible for upper-division and graduate courses in microbiology and immunology.

Comparative anatomy. The successful candidate will teach courses in comparative vertebrate anatomy, vertebrate zoology, and general biology or general zoology. Candidates with a specialization in herpetology and/or vertebrate mechanics are encouraged to apply.

Anatomy and physiology. The successful candidate will teach courses in anatomy and physiology to nursing and allied health students. They will also teach a general zoology or general biology course each semester.

Positions begin on 27 August 2008. All candidates must have a Ph.D. or be able to complete the Ph.D. by time of employment. Candidates teach 12 hours each semester, hold five office hours, advise biology majors, participate in Department and University activities, and engage in scholarly research and publishing in relevant journals. Applicants should submit a cover letter highlighting teaching and research experience, curriculum vitae, a statement of teaching philosophy and research goals, and letters of recommendation from three professional references.

Please mail materials to: **Dr. Dwight G. Smith, Chairman, Biology Department, Southern Connecticut State University, New Haven, CT 06515.** Review of applications will begin in November 2007. In order for your application to be given full consideration all materials must be received by December 31, 2007. The searches will continue until a suitable candidate is found.

Southern Connecticut State University is an Affirmative Action/Equal Opportunity Employer.

UCLA SCHOOL of PUBLIC HEALTH HIGH THROUGHPUT BSL3 LABORATORY. LABORATORY DIRECTOR for new Biosafety Level 3E Laboratory. Responsibilities: provide expert scientific guidance for development of automated assays for infectious diseases and quality assurance processes; oversee all business functions; train faculty, staff, and technicians on biosafety procedures and handling of select agents; supervision of laboratory facilities and staff. M.D. or Ph.D. in a life science or related field required. Required: eligibility for California licensure as a Clinical Laboratory Director and eligible for handling of select agents. Complete job description **website: http://www.ph.ucla.edu/pdfs/job_post_10172007a.pdf.** Please send curriculum vitae, list of three references, and letter of interest to: **Ms. Susan Fisher, Coordinator, Search for Laboratory Director; Office of the Dean, UCLA School of Public Health; P.O. Box 951772, Los Angeles, CA 90095-1772.** The Search Committee will begin considering applications November 1, 2007, and will continue until the position is filled. *Affirmative Action/Equal Opportunity Employer. Applications from women and underrepresented minority candidates are especially welcome.*

ASSISTANT PROFESSOR - ANATOMY

Tenure-track position expected to be available September 2008. Teaching responsibilities in histology for medical and dental students. Applicant should have a well-developed, fundable research program. Send curriculum vitae and two to three representative publications to: **John Young, Department of Anatomy, Howard University College of Medicine, 520 W. Street, N.W., Washington DC 20059 (e-mail: jyoung@howard.edu).** *Equal Opportunity Employer.*

POSITIONS OPEN

ASU ARIZONA STATE UNIVERSITY

ASSISTANT/ASSOCIATE PROFESSOR
Metabolic Biology - School of Life Sciences

The Translational Genomics Research Institute (TGen) and the Center for Metabolic Biology at Arizona State University seek highly motivated scientists for one or two faculty positions at the level of Assistant or Associate Professor. Research areas can include a broad range of interests in the areas of insulin resistance, type 2 diabetes mellitus and related complications, lipid metabolism, or cardiovascular disease. Candidates who are working at the interfaces among genomic, proteomic, and functional studies of proteins are especially encouraged to apply, and experimental approaches seeking links between genes that are candidates for disease processes and the function and abundance of the proteins encoded by these genes would be highly desirable. Two years of postdoctoral research experience and evidence of college level teaching experience desired.

The Diabetes, Cardiovascular and Metabolic Diseases Division at TGen, whose mission is to utilize genomic approaches to develop novel or improved diagnostic and treatment strategies for metabolic disorders, including diabetes and related complications, and the Center for Metabolic Biology, whose mission is to define the molecular mechanisms of insulin resistance are jointly recruiting these positions. The successful candidates will have appointments in the School of Life Sciences and the Center for Metabolic Biology at Arizona State University as well as TGen. Modern laboratory space, clinical research center, and proteomics and genomics instrumentation are available to the faculty. Generous startup packages will be provided. To apply, send letter of application highlighting your academic expertise and accomplishments, statement of research focus and accomplishments, statement of teaching philosophy and experience, current curriculum vitae, and three representative publications. Those applying for Assistant level should have three letters of recommendation sent to the **Chair, School of Life Sciences Metabolic Biology Search Committee** on letterhead and signed; those applying for Associate level should supply contact information (name, institution, address, e-mail address, and telephone number) for three references. Electronic applications are preferred (to **e-mail: elaine.finke@asu.edu),** but hard copies will be accepted if mailed to: **Chair, SoLS Metabolic Biology Search Committee, School of Life Sciences, P.O. Box 874501, Arizona State University, Tempe, AZ 85287-4501.**

Application deadline: December 1, 2007; if not filled, weekly thereafter until search is closed.

TGEN and Arizona State University are Affirmative Action, Equal Opportunity Employers committed to excellence through diversity. A background check is required for employment.

POSTDOCTORAL POSITION AVAILABLE in X-RAY CRYSTALLOGRAPHY

A Postdoctoral position is available in the Department of Biochemistry at Emory University (Atlanta, Georgia). The Laboratory will use structural biology to focus on transcriptional activation, on complexes between specific lipid transporters and their cognate nuclear receptor recipients, and on utilizing structure and ancestral gene resurrection to understand the evolution of novel function within proteins. The applicant is expected to have experience in X-ray crystallography, protein expression and purification, and strong general molecular biology skills. Interested candidates must have a Ph. D. and less than five years of postdoctoral experience in a related field. The successful candidate must be creative, motivated, and enjoy both working independently and in a collaborative setting. Please send (e-mail) cover letter, curriculum vitae, and the names and addresses of three references to: **Eric Ortlund, Ph.D., Assistant Professor. Telephone: 404-727-5014; fax: 404-727-2738. E-mail: eric.ortlund@emory.edu**

POSITIONS OPEN

BROWN

BROWN UNIVERSITY: SENIOR SEARCH for DIRECTOR of CENTER for ENVIRONMENTAL STUDIES

Brown University seeks a distinguished scholar with broad interdisciplinary interests in environmental issues to be the Director of the Center for Environmental Studies (CES). The Director will be responsible for overseeing faculty and programs in the CES, building on the Center's record of innovative interdisciplinary undergraduate and graduate education, actively promoting interaction between the CES and other environmental programs at Brown University, and enhancing the Center's presence in the community. CES interests encompass the humanities, natural sciences, public health, and social sciences. With Brown University's investments in the Plan for Academic Enrichment, the new CES Director will have unparalleled opportunities for building new initiatives based on the Center's strong tradition of innovation. For more information about the CES and new environmental research initiatives at Brown visit **website: http://envstudies.brown.edu/.**

Requirements include an outstanding scholarly record meriting a tenured appointment at the rank of **PROFESSOR**; commitment to excellence in undergraduate and graduate education; demonstrated leadership experience, vision, administrative ability, and communication skills in environmentally related areas. The candidate must also have the potential for productive interaction with faculty within the CES, cooperating departments, the Environmental Change Initiative, the Watson Institute for International Studies, the Population Studies and Training Center, the Initiative in Spatial Structures in the Social Sciences, and the Center for Environmental Health and Technology. This appointment will be at the rank of Professor, tenured in the appropriate department.

To apply, please send a letter of interest, current curriculum vitae, and names of five references to: **Search Committee, Center for Environmental Studies Director, P.O. Box 1943, Brown University, Providence, RI 02912-1943.** For further inquiries, please contact **e-mail: patricia-ann_caton@brown.edu.** Applications must be received by December 1, 2007, in order to receive full consideration. *Brown University is an Equal Employment Opportunity/Affirmative Action Employer.*

TWO POSITIONS
AQUATIC BIOLOGIST and CELL BIOLOGIST

Two tenure-track positions at **ASSISTANT PROFESSOR** level to begin August 2008. Responsibilities include courses in the major introductory sequence, college general studies curriculum, and an upper-level course in area of specialty. Actively involving undergraduates in ongoing research and commitment to the educational mission of a liberal arts Lutheran college is expected. Submit letter of application, curriculum vitae, complete transcripts, a statement of teaching philosophy and three letters of reference to: **Search Committee, Biology Department, Concordia College, Moorhead, MN 56562.** Application review will begin December 10, 2007, and will continue until the positions are filled. **Website: http://www.cord.edu/About/Jobs/faculty.php.** *Concordia College is an Equal Opportunity Employer seeking a diverse faculty.*

POSTDOCTORAL POSITIONS available to study regulation of cytokinesis in trypanosomes and miRNA depression of translation in *Giardia*. Research experience in molecular biology and cell biology is required. Must have a recent Ph.D. degree. Send curriculum vitae and names and addresses of three references to: **Prof. C.C. Wang, Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94158-2280. Fax: 415-476-3382; e-mail: ccwang@cgl.ucsf.edu.**

POSITIONS OPEN

CELL/MOLECULAR BIOLOGIST

Tenure-track **ASSISTANT PROFESSOR** position in cell/molecular biology. We seek applicants who will complement existing strengths in cell, developmental, molecular biology, and genetics. The successful applicant will be expected to maintain a funded research program, supervise student research, participate in teaching graduate and undergraduate courses, and provide service to the University. The Department has state-of-the-art facilities and offers competitive startup funds. The Department has 33 faculty, over 60 Ph.D./M.S. students, and approximately 1,000 majors **(website: http://zoology.muohio.edu/).** The cell, molecular, and structural biology research group includes over 30 faculty across four departments. Miami University (enrollment 22,000) is rated nationally as a highly selective public university. Send letter of application, curriculum vitae, statement of teaching and research interests, and three letters of recommendation to: **Dr. Douglas Meikle, Chair, Department of Zoology, Miami University, Oxford, OH 45056.** Review of applications will begin on 14 December 2007, and continue until the position is filled. Ph.D. required. Position available August 2008. **Telephone: 513-529-3100** or **e-mail: meikled@muohio.edu** for more information. For information regarding campus crime and safety, visit **website: http://www.muohio.edu/righttoknow.** Hard copy upon request. *Miami University offers Equal Opportunity in Employment and Education.*

VISITING ASSISTANT PROFESSOR. The Department of Biology at Denison University invites applications for a two-year position with emphasis in electrophysiology to begin August 2008. Research system and specialization within electrophysiology are open. A strong potential for excellence in teaching is essential. Ph.D. is required, postdoctoral experience, and demonstrated teaching ability are assets. This unique position carries a half-time teaching load and curricular development responsibilities. Teaching responsibilities are neurophysiology, introductory and advanced neuroscience, and introductory cell and molecular biology. Curricular development responsibilities include developing companion laboratories for the neuroscience courses. Denison offers funds for curricular development and support for student and faculty research. See the **website: http://www.denison.edu/biology** for a more detailed description of the position. Candidates should send a cover letter addressing their interest in liberal arts education and curricular development; curriculum vitae; statements of teaching philosophy and research interests; copies of transcripts (graduate and undergraduate); and the names, e-mail addresses, and telephone numbers of three references to: **Chair, Electrophysiology Search Committee, Biology Department, Denison University, Granville, OH 43023.** Review of applications will begin November 16, 2007. *Denison is an Affirmative Action/Equal Opportunity Employer. Women and minorities are especially encouraged to apply.*

ASSISTANT SCIENTIST (UNCLASSIFIED)

B.S. in biology, biochemistry, molecular biology, or biomedical sciences required. At least two years of laboratory experience in a biochemical, molecular biological, electrophysiological or/and other laboratory using computers and electronic instrumentation preferred. Basic knowledge in theory and practice of molecular biology, vertebrate physiology, and cell physiology desired. Send letter of application, curriculum vitae, brief statement of research interests/experience, with the contact information for three references to **e-mail: bthomps@vet.k-state.edu.** Screening of applications begins October 29, 2007, and continues until the position is filled.

Kansas State University is Equal Opportunity Employer. Kansas State University actively seeks diversity among its employees.

POSITIONS OPEN

Cleveland State University

PHARMACOLOGY

Cleveland State University invites applications for a tenure-track faculty position at the level of **ASSISTANT PROFESSOR in PHARMACOLOGY** starting in fall 2008. The Department of Chemistry offers B.S., M.S., and Ph.D. degrees. The Ph.D. Program specializes in clinical/bioanalytical chemistry and is jointly administered with the Cleveland Clinic Foundation.

Minimum qualifications: Ph.D. in pharmacology, biochemistry, pharmaceutical chemistry, chemistry, or a related field; ability to develop a nationally competitive research program in pharmaceutical chemistry; and ability to teach undergraduate and graduate pharmacology, pharmaceutical chemistry, and/or organic chemistry courses.

Preferred qualifications: postdoctoral experience, demonstrated accomplishments in research that complement existing expertise in the Department, and previous grant seeking and teaching experience.

Duties: teach undergraduate and graduate courses; research (supervising graduate students, submitting and administering grants, publishing); service to the Department, College, and University.

Qualified applicants should submit curriculum vitae, copies of undergraduate and graduate transcripts, and summaries of teaching and research interests (including a list of equipment needs and costs). Complete application and three letters of recommendation should be mailed to: **Dr. Valentin Gogonea, Chair, Chemistry Search Committee, Department of Chemistry, Cleveland State University, 2121 Euclid Avenue, Cleveland, OH 44115-2440.** Please, no e-mail applications. Review of the applications will begin on November 15, 2007, and will continue until the position is filled. For further information about the Department, visit the **website: http://www.csuohio.edu/chemistry.**

CSU is an Affirmative Action/Equal Opportunity Employer Institution committed to nondiscrimination in employment and education. Minorities/Females/Persons with Disabilities/Veterans encouraged.

The UNIVERSITY of TEXAS SOUTHWESTERN MEDICAL CENTER

ASSISTANT PROFESSORS. The Department of Physiology invites outstanding scientists with Ph.D., M.D., or equivalent degrees to apply for tenure-track Assistant Professor positions. Candidates who use innovative optical, mechanical, electrical, molecular biological, or computational methods with important applications to physiological systems, ranging from individual genes and proteins to cells and organs are encouraged to apply. However, the scientific excellence of the candidates is more important than the specific area of research.

These positions are part of the continuing growth of the Department at one of the country's leading academic medical centers and will be supported by significant laboratory space on our new campus, competitive salaries, and exceptional startup packages. The University of Texas (UT) Southwestern Medical Center is the scientific home to four Nobel Prize Laureates, 17 members of the National Academy of Sciences, and 19 members of the Institute of Medicine. UT Southwestern conducts more than 3,500 research projects annually totaling more than $350 million.

Applicants should submit curriculum vitae, a brief statement of research plans, and arrange to have three letters of reference sent to: **James Stull, Ph.D., c/o Gena McElyea, Department of Physiology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9040.** *UT Southwestern strongly encourages applications from women, minorities, and people with physical challenges. An Equal Opportunity Employer.*

UNCF • MERCK SCIENCE INITIATIVE

"A mind is a terrible thing to waste"

MERCK

UNDERGRADUATE SCIENCE RESEARCH SCHOLARSHIP AWARDS

- 15 Awards Annually
- Scholarships up to $25,000
- Two Summer Internships at a Merck Research Facility

An applicant must:

- Be a full-time student at any four-year college or university
- Have junior year academic status
- Major in a life or physical science (first professional degrees excluded)
- Have a minimum cumulative GPA of 3.3 (4.0 point scale)

GRADUATE SCIENCE RESEARCH DISSERTATION FELLOWSHIPS

- 12 Fellowships Annually
- Fellowship Stipends up to $42,000
- Department Grants of $10,000
- Support for 12-24 months

An applicant must:

- Be enrolled full-time in a Ph.D. or equivalent doctoral program in a biomedical life or physical science
- Be engaged in and within 1-3 years of completing dissertation research

POSTDOCTORAL SCIENCE RESEARCH FELLOWSHIPS

- 10 Fellowships Annually
- Fellowship Stipends up to $70,000
- Department Grants of $15,000
- Support for 12-24 months

An applicant must:

- Hold a Ph.D. or equivalent degree in a biomedical life or physical science
- Be appointed as a new or continuing postdoctoral fellow by the end of 2008 at an academic or non-academic research institution (private industrial laboratories are excluded)

Applicants must be African American (Black), U.S. citizens or permanent residents, and attending an institution in the U.S.A. Applications must be submitted online at www.uncf.org/merck/ by December 17, 2007

For more information, please contact your department chairperson or Jerry L. Bryant, Ph.D., at the **United Negro College Fund, Inc.**, 8260 Willow Oaks Corporate Drive, P.O. Box 10444, Fairfax, VA 22031-4511, by fax (703) 205-3574, or by e-mail at *uncfmerck@uncf.org*.

POSITIONS OPEN

Faculty Positions in Cardiovascular Biomedicine

CARDIOVASCULAR INNOVATION • INSTITUTE

The Cardiovascular Innovation Institute invites applications for tenure-track faculty positions at the **Assistant, Associate** and **Full Professor** level. Applicants are expected to have academic and/or industrial experience indicating promise of an exceptional future in interdisciplinary translational cardiovascular research and discovery. Investigators with a strong interest in translational and entrepreneurial activities working in the areas of heart failure, macro- and microvascular disease, cell-based therapies, inflammation/innate immunity, cardiovascular devices and experience in small animal models or pre-clinical large animal studies are encouraged to apply. Selected candidates for senior faculty positions will have demonstrated expertise in bioinstrumentation, biosensors or bioimaging and have the opportunity and resources to build a multi-investigator division.

The CII is a non-profit partnership between the University of Louisville and Jewish Hospital dedicated to discovering and developing the next generation of heart and vascular health care technologies. Institute investigators share appointments with the UofL and/or Jewish Hospital and work in a new state-of-the-art research building in a highly collaborative environment with outstanding opportunities to translate research through clinical partnerships and industrial collaborations.

The CII is located in Louisville, a progressive city situated along the scenic Ohio River with a thriving cultural scene and a variety of outdoor recreation opportunities.

Applicants should submit a cover letter describing research interests and CV to: **Stuart K. Williams, PhD, Scientific Director, Cardiovascular Innovation Institute, Louisville, KY, 40202** or by email to **stu.williams@louisville.edu**. Consideration of applications will begin immediately and positions will be open until filled.

The University of Louisville is an Affirmative Action, Equal Opportunity, Americans with Disabilities Employer, committed to diversity, and in that spirit, seeks applications from a broad variety of candidates.

POSITIONS OPEN

UNIVERSITY OF ALASKA FAIRBANKS

The School of Fisheries and Ocean Sciences (SFOS) at the University of Alaska Fairbanks (UAF) invites applications for two **MARINE BIOLOGIST** vacancies specializing in early life ecology and mammalogy/population genetics. Both positions are **ASSISTANT/ASSOCIATE PROFESSOR,** tenure-track faculty positions within the SFOS Institute of Marine Science located in Fairbanks, Alaska. To learn more about the School please visit **website: http://www.sfos.uaf.edu.** Complete position information can be found at **website: https://www.uakjobs.com,** reference postings 0054202 and 0054183.

FACULTY POSITION in CELL and MOLECULAR BIOMECHANICS
Biomedical Engineering
University of California, Davis

The College of Engineering at University of California (UC) Davis invites applications from qualified candidates for a tenured position at the **ASSOCIATE or FULL PROFESSOR** rank commensurate with the candidate's accomplishments. The position will be in the Department of Biomedical Engineering and will focus on cell and molecular aspects of orthopaedic biomechanics. It aims to interweave medical applications with fundamental research that bridge the cell and molecular systems and musculoskeletal biomechanics research tracks of the Biomedical Engineering Program at UC Davis. Exceptional candidates in other areas of research related to biomedical engineering will also be considered. Candidates should have a Ph.D. degree in biomedical engineering or a related field, a commitment to excellence in teaching, a publication record that demonstrates outstanding research, and potential for administrative and programmatic leadership. The hire will be expected to develop an extramurally funded research program, forge strong interactions with the UC Davis Medical School, contribute to core undergraduate and graduate courses, and assist in establishing an innovative multidisciplinary curriculum in the field of cell and molecular musculoskeletal biomechanics.

UC Davis is 12th among U.S. public universities in research funding, and the College of Engineering is ranked among the top ten public engineering colleges in the nation. Davis is a pleasant, family-oriented community in a college-town setting with excellent public schools and a mild climate. Davis' ideal location is just 15 miles from California's capital city of Sacramento and within easy driving distance of the Sierra Nevada Mountains, San Francisco, Silicon Valley, wine country, and the Pacific Coastal areas.

Interested candidates should submit all materials via the web-based online submission system **(website: https://jobs.bme.ucdavis.edu).** Required materials include a statement of research and teaching interests (this should include information about mentoring women, minorities, students with disabilities, or other underrepresented groups), curriculum vitae, three to five representative publications, and the names and contact information of at least five references who have agreed to write letters of reference. Inquiries can be directed to the **Chair of the Search Committee** at **e-mail: biomedicalengineering@ucdavis.edu.** The review of applications will begin on December 15, 2007. However, the position will remain open until filled. The UC Davis College of Engineering **(website: http://engineering.ucdavis.edu)** is committed to building a diverse faculty, staff, and student body as it responds to the changing population and educational needs of California and the nation.

UC Davis is an Affirmative Action/Equal Employment Opportunity Employer and is dedicated to recruiting a diverse faculty community. We welcome all qualified applicants to apply, including women, minorities, individuals with disabilities and veterans.

POSITIONS OPEN

ASSOCIATE/FULL PROFESSOR
Molecular Immunology/Immunogenetics
Position Announcement

The Department of Veterinary Pathobiology, Texas A&M University invites applications for a tenure-track, fully funded, 12-month Associate/Full Professor position in molecular immunology or immunogenetics, with 75 percent effort in research and 25 percent in teaching/service. Successful candidates must hold a Ph.D. in immunology/microbiology, molecular biology or genetics, have an established and funded research program with a significant record of publication, grantsmanship, and graduate student/postdoctoral training. Rank, salary, and startup is contingent upon experience and national reputation. Application review begins December 1, 2007, and continues until the position is filled. Candidates should submit a statement of career goals and research interests, curriculum vitae, summary of current and planned research support, experience in training graduate students and postdoctoral fellows, teaching interests and experience, with the names and addresses of three references to **e-mail: cvoelker@cvm.tamu.edu.** Written applications can be sent to: **Ms. Cynthia Voelker, Department of Veterinary Pathobiology, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843-4467.** Inquiries regarding the position may be e-mailed to **Dr. Guan Zhu (Search Chair)** at **e-mail: gzhu@cvm.tamu.edu.** Detailed information regarding the position, Department, and College can be found at **website: http://www.cvm.tamu.edu.** *Texas A&M University is an Equal Opportunity/Affirmative Action Employer.*

BIOLOGY of CANCER
University of South Carolina

The Department of Biological Sciences at the University of South Carolina (USC) invites applications for a tenure-track position at the rank of **ASSISTANT PROFESSOR** in the broad area of the biology of cancer. Particular interest will be applied to individuals using animal models to further our understanding of the physiological mechanisms of cancer development and progression at the molecular, cellular, histological, or organismal level. The successful candidate will interact with a growing research group within USC's Center for Colon Cancer Research **(website: http://cccr.sc.edu/).** Additional hires at both the junior and senior level are anticipated in this area over the next several years, both within the Department of Biological Sciences and in other departments. Candidates should have a M.D. or Ph.D., along with postdoctoral experience, in an appropriate area of biomedical science. The successful individual will be expected to establish an independent, extramurally funded research program. In addition, he/she will be responsible for teaching an undergraduate course in general physiology, and an undergraduate or graduate course appropriate to his/her research area. Additional information on the Department of Biological Sciences can be found at **website: http://www.biol.sc.edu/.** Interested persons should send curriculum vitae, a summary of research accomplishments and future plans, a statement of teaching interests, copies of representative publications, and three letters of recommendation to: **Dr. Franklin G. Berger, Biology of Cancer Search Committee, Department of Biological Sciences, University of South Carolina, Columbia, SC 29208.** To ensure full consideration, applications should be submitted by December 15, 2007. *The University of South Carolina is an Affirmative Action, Equal Opportunity Employer, and does not discriminate in educational or employment opportunities or decisions for qualified persons on the basis of race, color, religion, sex, national origin, age, disability, sexual orientation, or veteran status. Minorities and women are encouraged to apply.*

POSITIONS OPEN

YALE SCHOOL of MEDICINE: FACULTY POSITIONS in a NEW PROGRAM on ENERGY METABOLISM and OBESITY

The Section of Comparative Medicine at Yale University School of Medicine seeks up to three new faculty members to join a new interdisciplinary research program focused on the neurobiology of energy metabolism and obesity. The Section has significant strength in areas including mouse mutagenesis, pathologic phenotyping, and laboratory animal medicine. It is developing the new program in close conjunction with other Departments including Medicine, Neurobiology, Pharmacology, and Psychiatry, and program faculty will have the opportunity to collaborate actively with outstanding basic and clinical research groups in the areas of metabolism, neurobiology, aging, and immunology.

Candidates (holding D.V.M., M.D., or Ph.D. degrees) should possess a strong research and funding record, and will be appointed at the level of **ASSISTANT, ASSOCIATE, or FULL PROFESSOR,** depending upon qualifications. Interested applicants should send curriculum vitae, research plan, and a list of three references to:

Tamas Horvath, D.V.M., Ph.D.
Professor and Chair, Section of Comparative Medicine
Yale University School of Medicine
P.O. Box 208016
New Haven, CT 06520-8016
E-mail: valeria.krizsan@yale.edu

The evaluation of applications will begin immediately and continue until the positions have been filled. Yale University is an Equal Opportunity/Affirmative Action Employer.

POSTDOCTORAL POSITIONS. Several positions are immediately available to study the role of lipoxygenases/eicosanoids in angiogenesis and vascular wall remodeling. Experience with animal models of angiogenesis, restenosis, and/or molecular cloning is highly desirable. Based on experience competitive salaries are offered. Interested and highly motivated candidates with Ph.D., M.D., or M.D./Ph.D. degree should send curriculum vitae and names and addresses of three references to: **G.N. Rao, Ph.D., Department of Physiology, University of Tennessee Health Science Center, 894 Union Avenue, Memphis, TN 38163. E-mail: grao@physio1.utmem.edu.** *The University of Tennessee is an Equal Employment Opportunity/Affirmative Action Title VI/Title IX/Section 504/ADA/ADEA Institution in the provision of its education and employment programs and services.*

Additional job postings not featured in this issue can be viewed online at website: http://www.sciencecareers.org. New jobs are added daily!

MARKETPLACE